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LIVER INJURY IN THYROTOXICOSIS AS EVIDENCED BY DECREASED FUNCTIONAL EFFICIENCY

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AND

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It has long been known that injury to the liver may occur in severe cases of thyrotoxicosis and the appearance of jaundice has been looked on as a grave prognostic sign, but that liver injury is present with any considerable frequency or that it plays any important consistent rôle in the disease has scarcely been considered. It has been suggested,¹ however, that the decreased glucose tolerance occurring in cases of thyrotoxicosis, a phenomenon not as yet adequately explained, might be the result of damage to the liver.

With this possibility in mind we have made a combined study of the functional efficiency of the liver and of the glucose tolerance in cases of thyrotoxicosis² to determine whether damage to the liver occurs with any important frequency in this disease and whether it bears any relation to the glucose tolerance. Results of this study show that injury to the liver occurs in a surprisingly large number of instances but fail to show any constant or causal relation between the liver damage and the decreased glucose tolerance.

METHOD

The material studied consisted of a fairly consecutive series of forty-eight patients admitted to the medical service with a diagnosis of thyrotoxicosis. The patients were studied in the manner usual in such cases, and in addition tests of liver function and of the glucose tolerance were made in twenty-seven instances. In the remaining

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1 Sanger, B. J., and Hun, E. J. The Glucose Mobilization Rate in Hyperthyroidism, *Arch. Int. Med.* **30**: 397 (Sept.) 1922.

2 The word thyrotoxicosis is used in this paper to mean diseases of the thyroid gland, neoplasm excepted, characteristically associated with an increased basal metabolism. It includes the conditions variously known as exophthalmic goiter, hyperthyroidism, toxic adenoma and adenoma with hyperthyroidism.

twenty-one the liver function was tested but the glucose tolerance was not determined. When both the liver function and the glucose tolerance were tested both tests were performed at as nearly the same time as possible, usually within a week of each other. In two cases the tests were done four weeks and in one case two weeks apart. An attempt was made to test these functions during the more severe stages of the disease, usually soon after admission, in order to avoid negative findings due to improvement under treatment. In view of the well known cardiac complications of the disease and the possibility of a disturbed liver function due to cardiac failure, patients presenting signs of any considerable heart failure were not, as a rule, used in this study. In one or two instances such patients were studied and the test of liver function deferred until compensation had been clearly established. Patients presenting complications likely to influence liver function were not used.

The functional efficiency of the liver was determined by means of the phenoltetrachlorophthalein test as modified by Rosenthal³ and in a few instances by the levulose tolerance test, the hemoclastic crisis test of Widal, Abrami and Iancovescu,⁴ and by the determination of the concentration of the bilirubin in the blood serum.

The Rosenthal modification of the phenoltetrachlorophthalein test was adopted as the standard test of liver function. Five milligrams of the dye per kilogram of body weight, well diluted with warm physiologic sodium chlorid solution, were injected intravenously by the use of a three-way stop-cock and syringe apparatus or with simply a 50 c.c. Luer syringe. Blood was subsequently withdrawn from the opposite arm for examination. In the earlier cases samples of blood for the determination of the dye concentration were withdrawn at fifteen minute and one hour intervals after injection, as in the original Rosenthal technic. Later the hour specimen alone was drawn. While the fifteen minute specimen is useful, it was felt that the hour specimen gave the essential information and that the additional information gained by the use of the fifteen minute specimen did not justify the extra venipuncture in these cases.

The determination of the percentage of the dye in the blood serum was first done by the original Rosenthal technic, later the modifications of Bogen,⁵ Blum and Rosenau⁶ and the later modification of Rosen-

3 Rosenthal, S. M. A New Method of Testing Liver Function with Phenoltetrachlorophthalein, *J. A. M. A.* **79** 2151 (Dec 23) 1922

4 Widal, F., Abrami, P., and Iancovescu, V. Digestion Hemoclastic Test in the Study of Hepatic Insufficiency, *Presse med.* **28** 893, 1920

5 Bogen, E. A Clinical Test for Liver Function, *J. Clin. & Lab. Med.* **8** 619 (June) 1923

6 Blum, W., and Rosenau, W. H. The Reaction of the Liver to Phenoltetrachlorophthalein in Early Obstructive Jaundice, *Arch. Int. Med.* **34** 446 (Oct) 1924

thal,⁷ similar to that of Bogen, were used. While in an occasional case none of these methods are entirely satisfactory the later method of Rosenthal was found to be the most generally useful. The acetone method of Blum and Rosenow has, in our hands, frequently failed completely to remove all the coloring matter from the serum. The exact cause of this failure has not been determined and may not be inherent in the method itself.

A retention of 3 per cent or more of the dye in the blood serum at the end of one hour has been considered evidence of an impairment of liver function. While this figure may seem rather low, we believe it is justified by the practically entire absence of retained dye in the serum of a number of normal controls and a large number of patients with miscellaneous diseases who have given a normal response to the test.

A word regarding reactions seems advisable. A general reaction occurred five times, or in 12.5 per cent of the patients, in this series and in a total of some ninety tests by this method general reactions have occurred only seven times. The typical general reaction is characterized by a more or less severe chill, coming on with considerable regularity about one hour after the injection of the dye, and followed by a moderately high fever. The patient complains of general body pain and malaise. Occasionally the fever or the chill is lacking. Nausea and vomiting were not noted and diarrhea occurred in only a single case. Not infrequently the patient noticed a feeling of increased well-being after the reaction. Thrombosis of the vein at the site of injection occurred but once in all the times the test has been performed.

The levulose tolerance test of liver function was performed as follows. A sample of blood was obtained following a twelve hour fast and the amount of blood sugar determined. Fifty grams of levulose dissolved in two glasses of lemonade was then given by mouth and samples of blood obtained at fifteen minute, one hour and two hour intervals and their sugar content determined. The same amount (50 gm.) of levulose was given in every case since the relation of the amount of levulose to the weight seems, within ordinary limits, to be unimportant.⁸ Failure of the blood sugar concentration to rise above 0.135 per cent and the return of the blood sugar concentration to a normal or near normal figure at the end of two hours was considered to be a normal response.⁸ The cost of the levulose constitutes a considerable bar to the frequent use of the test.

⁷ Rosenthal, S. M. The Phenoltetrachlorophthalein Test for Hepatic Function, Recent Studies with the Author's Method, *J. A. M. A.* **83** 1049 (Oct. 4) 1924.

⁸ Tallerman, K. H. Levulose Test for Liver Efficiency, Investigation of Hepatic Condition in Pregnancy, *Quart. J. Med.* **17** 37 (Oct.) 1923.

Widal's hemoclastic crisis test of liver function was performed as follows. The patient was fasted twelve hours and a leukocyte count was made. The patient was then given a glass of milk and a leukocyte count was made at thirty minute intervals for two hours. A drop in the leukocyte count below the fasting level was considered evidence of a disturbance in liver function. Widal and Abram⁹ have recently stated that this method of performing the test differs from the technic described by them and Iancovesco and will lead to incorrect conclusions.

The bilirubin content of the blood serum was determined according to the method described by Stettin¹⁰ and by Bernheim,¹¹ in this procedure a Duboscq colorimeter with special small cups was used instead of a Bock-Benedict. An icterus index of 6, as given by Bernheim, was considered the upper limit of normal.

The glucose tolerance test was performed in the following manner. A sample of blood was obtained after a twelve hour fast and 1.75 gm of glucose per kilogram of body weight in two glasses of lemonade was then given by mouth. Samples of blood were drawn at fifteen minute, one hour and two hour intervals after the administration of the glucose and their sugar content was determined. Failure of the blood sugar level to rise above 0.2 per cent, the occurrence of the maximum concentration by the end of one hour and the return of the blood sugar concentration to the normal or nearly normal fasting level (0.12 per cent or less) within two hours was considered a normal response. All blood sugar determinations were done by the method of Folin and Wu.¹²

Certain features of this method of testing the glucose tolerance demand comment. The oral administration of the glucose has been criticized because of the variations in absorption of the glucose from the alimentary tract. Various procedures have been suggested to avoid this possible source of error, particularly the use of the intravenous method of administering the glucose. We decided against the use of this procedure for the following reasons. First, since our studies were particularly concerned with the liver it seemed advisable that the blood sugar concentrations be determined following normal absorption of the glucose from the intestine and transport through the portal circulation.

9 Widal, F, and Abram, P. The Digestion Hemoclastic Test in the Study of Hepatic Insufficiency, *J A M A* **84** 1002 (March 28) 1925.

10 Stettin, D. Surgical Value of Estimation of Bile Pigmentation (Icterus Index) of Blood Serum, *Ann Surg* **76** 191 (Aug) 1922.

11 Bernheim, A. R. The Icterus Index (a Quantitative Estimation of Bilirubinemia). An Aid in Diagnosis and Prognosis, *J A M A* **84** 291 (Jan 26) 1924.

12 Folin, Otto. Laboratory Manual of Biological Chemistry, Ed 3, New York, D Appleton & Co., 1922.

to the liver. Second, there is evidence¹³ that the amount and rate of glucose absorbed, within rather wide limits, affects the curve of blood sugar concentration but little. The changes in blood sugar concentration following glucose ingestion are not solely and directly dependent on the character of the glucose absorption. We have had some evidence of the truth of this assertion in certain patients who vomited a part of their glucose and still showed markedly abnormal curves. It is, of course, recognized that the vomiting of any considerable amount might very well affect the result, especially in cases with only a slight decrease of tolerance. If the foregoing be true, however, there is little error introduced by the failure of complete absorption of the glucose. Third, it has been shown that ordinarily the absorption of glucose from the intestine is a fairly constant and consistent process¹⁴. It would seem that in thyrotoxic states, in which the alimentation is characteristically good in the absence of diarrhea, absorption would be particularly rapid and complete. In order to avoid as far as possible errors due to disturbances in absorption, care was taken not to test the glucose tolerance during a period of gastro-intestinal upset, particularly during an attack of diarrhea.

The time periods at which samples of blood were taken are probably not the best for obtaining the most accurate information regarding abnormalities in the curve of blood sugar concentration. Samples taken at thirty minute, one hour and two hour intervals after the injection of the glucose would probably give a more exact picture of the process. The procedure used was adopted to permit comparison with work previously done by others.¹

The determination of the basal metabolic rates of the patients in this series was done with the Roth modification of the Benedict portable metabolism apparatus and the usual standard technic. The graphic method was used in some of the later cases. Basal metabolic rates are expressed as percentage of deviation from normal (tables of Aub and Dubois).

RESULTS

Table 1 presents a summary of the data obtained. Of the forty-eight patients studied two failed to show definite evidence of thyrotoxicosis and in two cases the test of liver function was unsatisfactory. These four cases have been eliminated from the series and from Table 1, leaving forty-four cases for consideration.

13 Maclean, H., and de Wesselow, O. L. V. The Estimation of Sugar Tolerance, *Quart J Med* **14** 103 (Jan) 1921. Foster, G. L. Studies on Carbohydrate Metabolism, II, An Interpretation of the Blood Sugar Phenomena Following the Ingestion of Glucose, *J Biol Chem* **55** 303 (Feb) 1923.

14 Janney, N. W., and Isaacson, V. I. A Blood Sugar Tolerance Test, *J A M A* **70** 1131 (April 20) 1918.

TABLE 1—Summary of Data

Case	Age	Sex*	Diagnosis	Loss of Weight (Kg)	Basal Metabolic Rate, per Cent, †		Glucose Tolerance Index‡	Liver Function, § Retained Dye, per Cent,		Remarks
					Maximum	Minimum		15 Min-utes	60 Min-utes	
1	42	♂	Exophthalmic goiter	4.5	56.0	12.5	26.5	10	5	
2	55	♀	Exophthalmic goiter	9.0	36.0		20.4	8	5	Erysipelas, necropsy
3	32	♀	Hyperthyroid	3.6	21.0	17.5	17.4	4	2	Rubella
4	16	♀	Exophthalmic goiter	11.8	73.0		16.4	12	10	Jaundice, pneumonia, died
5	32	♀	Toxic adenoma	11.3	50.5	23.0	10.3	4	0	Mastoiditis
6	38	♀	Exophthalmic goiter		70.0	37.5	12.8	8	8	Jaundice, died
7	64	♂	Exophthalmic goiter	27.2	16.5	12.0	13.8	8	2	
8	20	♀	Hyperthyroid	10.0	24.6	16.5	16.6	6	0	
9	40	♀	Exophthalmic goiter		35.5		18.7	4	0	Liver palpable
10	46	♂	Exophthalmic goiter	31.8	39.5	14.0	14.5	10	5	Jaundice, auricular fibrillation, diarrhea
11	54	♀	Toxic adenoma	13.6	49.5			7	73 (R)	Auricular fibrillation, Wassermann reaction 4+
12	60	♂	Exophthalmic goiter	15.0	82.0		14.0	12		
13	37	♀	Toxic adenoma	4.5	64.0	38.5	20.2	7	4	Vomited part of glucose
14	44	♀	Exophthalmic goiter	11.3	78.0	36.0	10.4	4	0	Liver palpable
15	58	♀	Exophthalmic goiter	6.8	60.0	36.0		3	0	Auricular fibrillation
16	41	♀	Exophthalmic goiter	13.1	23.0	13.5	6.6	4	0	
17	36	♂	Exophthalmic goiter	11.8	105.5	37.2	16.3	4	2.5	Auricular fibrillation
18	60	♀	Toxic adenoma	7.7	50.5	9.8	13.2	7	0	
19	42	♀	Toxic adenoma	9.0	26.5			6	0 (R)	
20	19	♀	Exophthalmic goiter	18.1	66.0	34.5	9.6	5	0	
21	33	♀	Exophthalmic goiter	12.7	75.0	52.0	13.8	6	2.5	
22	30	♀	Exophthalmic goiter	5.0	68.0	61.5		6	1	
23	48	♀	Exophthalmic goiter	8.1	70.0	17.5	8.9	8	4	Myxedema, diphtheria
24	49	♀	Toxic adenoma	13.6	92.0	62.0	9.9		2	
25	49	♀	Exophthalmic goiter	13.6	61.0	40.5	14.9		3+	Diarrhea
26	50	♀	Exophthalmic goiter	11.8	77.5	47.0	12.8		4	Auricular fibrillation
27	32	♂	Exophthalmic goiter	11.8	38.0	8.0	33.5		0	Glycosuria
28	43	♀	Exophthalmic goiter	4.5	29.0	20.5	8.5	8	4	
29	25	♀	Toxic adenoma	9.0	21.0		15.6	9	3+	
30	45	♀	Exophthalmic goiter	18.1	70.0		Unsatis	10	10	Vomited glucose, jaundice, necropsy
31	38	♀	Exophthalmic goiter	14.5	108.0	51.0	12.0	3	0 (R)	
32	42	♀	Exophthalmic goiter	38.6	50.0	39.5		2	0	Cystitis
33	44	♀	Toxic adenoma	20.0	63.5	8.0			4	Jaundice
34	19	♀	Exophthalmic goiter	9.0	78.0	31.0			1	
35	36	♀	Toxic adenoma	4.0	54.0	19.5			5	
36	51	♀	Toxic adenoma		16.0	9.5			3	Auricular fibrillation
37	54	♂	Toxic adenoma		25.0	9.2			3+(R)	Auricular fibrillation
38	49	♀	Exophthalmic goiter	7.2	73.5	34.8			5	Jaundice, auricular fibrillation
39	53	♀	Toxic adenoma	7.2	44.0	34.0			5	
40	38	♀	Toxic adenoma	34.0	93.0	28.0			10	Jaundice
41	45	♀	Toxic adenoma	2.7	45.7		7.1		5	
42	34	♂	Exophthalmic goiter	4.5	50.0	13.6			5	Liver palpable
43	32	♂	Exophthalmic goiter	10.0	91.0	21.5			3	
44	18	♀	Exophthalmic goiter	23.6	86.5	34.5			2	

* In this table ♂ indicates male, ♀ female

† Expressed as percentage of deviation from normal, tables of Aub and Dubois

‡ Description of method by which index is obtained is given in text Ten or below is considered normal

§ Phenoltetrachlorophthalein method R indicates reaction

An examination of the results shows that of the forty-four patients twenty-two showed evidence of liver injury according to the standard test of liver function (phenoltetrachlorphthalein) used. In these twenty-two patients the percentage of dye retained in the blood serum at one hour varied from 3 to 10 per cent. In one other patient the result was doubtful. In addition to the findings with the phenoltetrachlorphthalein test the levulose tolerance test gave evidence of damage to the liver in three of the seven cases in which it was tried, the Widal test in three out of eight cases, and the bilirubin content of the blood serum was found increased in seven of the nine cases in which a satisfactory estimation of its concentration was obtained.

Strictly speaking, in nearly all the cases tested the glucose tolerance was more or less abnormal in respect to one or the other characteristic features of the curve of sugar concentration of the blood, namely, the height of the rise, the time of maximum concentration or the time of return to a normal concentration. To aid in the analysis of the results we have expressed this abnormality numerically by measuring the area subtended by the blood sugar curves in a manner described below. The figure so obtained we have called the glucose tolerance index. According to this arbitrary method, which agrees quite closely with the ordinary method of interpreting blood sugar curves in glucose tolerance determinations, the cases in this series with a glucose tolerance index figure of 20 or over are considered markedly abnormal, those with an index of from 14 to 20, moderately abnormal, those with an index of 10 or over, slightly abnormal, and those below 10, normal. So classified, four patients had a marked, nine a moderate and eight a slight decrease in glucose tolerance. Six of the patients had a normal glucose tolerance. In this normal group are placed two patients whose classification is doubtful. One (Case 20) seemed to have a slightly abnormal curve but according to the method of classification used is classified as normal. The other (Case 16) lacked the one hour blood sample. The determination of the glucose tolerance was unsatisfactory in one instance (Case 30).

Six of the patients in this series died, Patients 2, 4, 6, 24, 27 and 30. In five cases, including one patient who died after operation, Patient 24, death was apparently due directly or indirectly to the thyroid disease. One patient (Case 2) died during an attack of erysipelas. Four of the patients who died were among those in this series who gave evidence of liver injury. Three of these had been jaundiced. Necropsy was performed in two instances (Cases 24 and 30) and in both the patients had presented evidence of liver damage. One (Case 30) showed evidence of a mild chronic cholecystitis and a chronic passive congestion of the liver. The liver was of about normal size, the capsule thin and smooth. On section marked chronic passive

congestion and some fatty changes were seen. The cut section was yellowish, reddish and brown. The lobules appeared normal in size. The gallbladder was thin walled and adherent to the colon at the hepatic flexure. No gallstones were found.

In the other (Case 2) the liver was about normal in size and brown. The lobules were easily seen on the surface and more easily seen on section. The liver was congested and of the nutmeg variety.

In both cases the pathologic diagnosis of the thyroid condition was exophthalmic goiter.

ANALYSIS OF RESULTS

Analysis of the twenty-eight cases in which tests of both liver function and the glucose tolerance were done fails to show any clear relation between the presence and degree of liver damage and the glucose tolerance. Ten cases showed a decreased glucose tolerance and evidence of liver injury. Ten had a decreased glucose tolerance but gave no evidence of damage to the liver. Three cases showed evidence of liver injury but no decrease in the glucose tolerance. In four cases both glucose tolerance and liver function were normal, and in one case the glucose tolerance test was unsatisfactory. It should also be noted that in the cases with decreased glucose tolerance and evidence of damage to the liver there was no relation between the degree of liver damage and the degree of decrease in glucose tolerance.

A comparison of the liver function and the glucose tolerance is shown in Table 2. A word of explanation is necessary in regard to the "index of glucose tolerance" included in Table 2. As stated above, curves of the blood sugar concentrations following the ingestion of glucose may vary from the normal in one or more of their characteristic features. This makes it difficult to express the degree of abnormality in a single numerical expression. To solve this difficulty we have employed a method described by Lamson¹⁵ by which the area subtended by a curve is used to express numerically the degree of abnormality of the function represented by that curve. The blood sugar concentrations were plotted on coordinate paper, ruled twenty divisions to the inch, where one-fourth ordinal inch represented 10 mg. of sugar and one-fourth abscissal inch represented five minutes. The area subtended by such a curve was measured and the figure thus obtained (square inches), when compared with the figure obtained by measuring the area subtended by a maximum "normal" curve, indicates the degree of abnormality of the glucose tolerance. This figure has been called by us the "glucose tolerance index." The method is not entirely exact as

15 Lamson, P. D., Gardner, G. H., Gustafson, R. K., Maire, E. D., McLean, A. J., and Wells, H. S. The Pharmacology and Toxicology of Carbon Tetrachloride, *J. Pharm. & Exper. Therap.* **22**: 215 (Nov.) 1923.

the curves that are slightly abnormal, particularly as regards the time of maximum concentration of the blood sugar, may give figures that fall within the maximum figures of normal. It is, however, we believe, sufficiently accurate for our purpose. As stated above, a glucose tolerance index of 10 or below is considered normal in this study.

With the figures so obtained a statistical study¹⁶ has been made of the data in Table 2 to determine further if any relation exists between the glucose tolerance, thus expressed, and the liver function.

The average of the indexes of glucose tolerance is 14.6 and the average liver function expressed in percentage of dye retained at one hour is 2.7. The standard deviation of the index of glucose tolerance is

TABLE 2—Comparison of Glucose Tolerance and Liver Function*

No	Case	Glucose Tolerance Blood Sugar Concentrations, Mg Per 100 C c				Index Glucose Tolerance	Liver Function †
		Fasting	15 Minutes	1 Hour	2 Hours		
1	5	0.083	0.111	0.174	0.166	10.3	0
2	8	0.136	0.187	0.200	0.200	16.6	0
3	9	0.110		0.250	0.174	18.7	0
4	14		0.136	0.187	0.120	10.4	0
5	16	0.103	0.141		0.132	6.68	0
6	18	0.096	0.226	0.186	0.100	13.2	0
7	20	0.089	0.103	0.187	0.132	9.6	0
8	27	0.136		0.370	0.340	33.5	0
9	31	0.111	0.137	0.204	0.125	12.0	0
10	3	0.103	0.142	0.230	0.180	17.4	2
11	7	0.12	0.200	0.200	0.174	13.8	2
12	24	0.083	0.166	0.150	0.111	9.9	2
13	17	0.160	0.200	0.260		16.3	2.5
14	21	0.077	0.125	0.217	0.172	13.8	2.5
15	12	0.100	0.200(40 min.)	0.200	0.214	14.0	12(15 min.)
16	25	0.105	0.157	0.229	0.142	14.9	3
17	29	0.111	0.192	0.192	0.190	15.6	3
18	13	0.093	0.250	0.250	0.127	20.2	4
19	23	0.080	0.120	0.176	0.118	8.9	4
20	26	0.103	0.153	0.184	0.168	12.8	4
21	28	0.120	0.136	0.161	0.111	8.5	4
22	41	0.100	0.202	0.113	0.090	7.1	—5
23	2	0.136	0.166	0.230	0.270	20.4	5
24	10	0.120	0.150	0.250	0.100	14.5	5
25	1	0.100	0.250	0.250	0.300	26.5	5
26	6	0.136	0.150	0.187	0.166	12.8	8
27	4	0.080	0.120	0.250	0.187	16.4	10
28	30	Unsatisfactory					10

* Table is arranged in the order of increasing degree of liver injury.

† Description of the method by which this index is obtained is given in text. Ten or below is considered normal.

‡ Phenoltetrachlorophthalein method, percentage of dye retained at one hour.

§ The index in this case is misleading because of the loss of the hour specimen.

6.266 and of the liver function 2.628. The coefficient of correlation of the glucose tolerance and liver function is 0.3738 ± 0.1137 .

In Figure 1 this lack of correlation is shown.¹⁷ This figure is a scatter diagram of the deviations from the mean divided by the standard deviation of the index of glucose tolerance and of the liver function. The results are plotted against each other.

16 Hodges, P. C., and Eyster, J. A. E. Estimation of Cardiac Area in Man, *Am J Roentgenol* **12** 252 (Sept.) 1924.

17 Davis, H. W., Meakins, J., and Sands, J. The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood, V, The Blood Gases and Circulation Rate in Hyperthyroidism, *Heart* **11** 299, 1924.

It might be expected that some relation would be found to exist between the liver injury and the basal metabolism since it would seem natural for liver injury to occur in the more severe cases in which the metabolic rate would tend to be high. There was a slight tendency to such a relation but it was not constant. Of the twenty-two patients presenting evidence of liver damage fifteen, or 69 per cent, had a maximum basal rate of plus 50 per cent or over. There was, however, considerable variation so that the average basal rate of plus 56.2 per

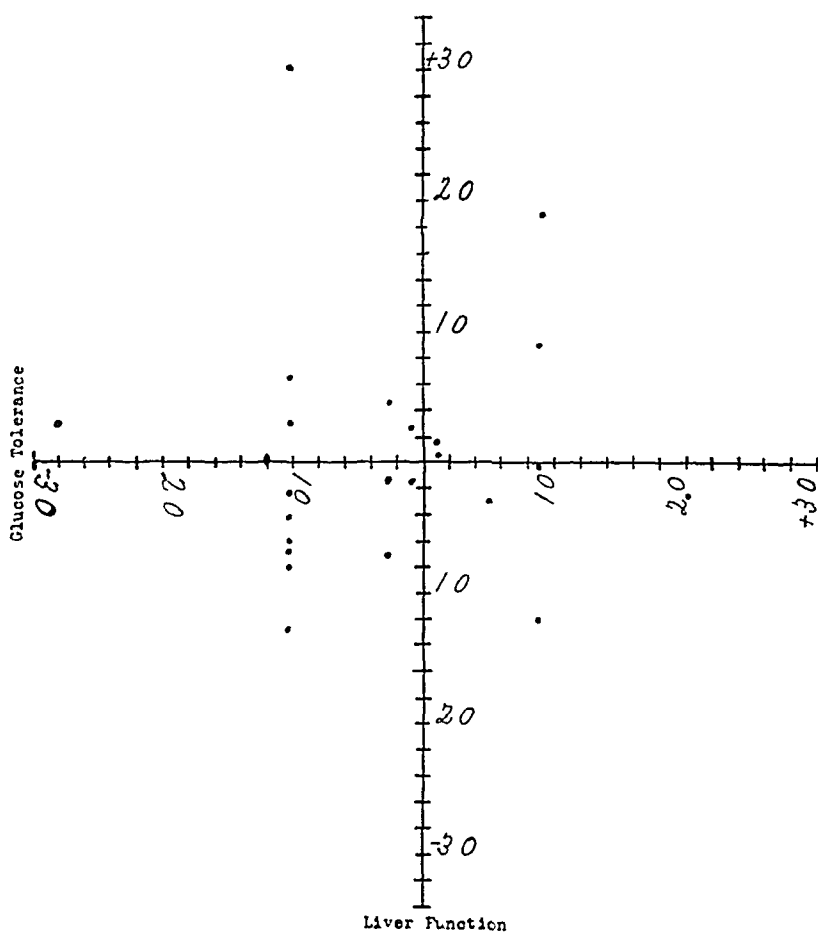


Fig 1—Comparison between the deviations from mean divided by standard deviation of glucose tolerance expressed as "glucose tolerance index" and liver function expressed in percentage of dye retained at one hour (from Table 2), Cases 12 and 28 have been omitted

cent is scarcely a true representation of the facts and several cases with a relatively low basal rate showed evidence of liver damage (Cases 28, 29, 38 and 37). Of equal importance, of the twenty-two patients without evidence of liver damage nearly as many (fourteen) had a maximum basal metabolic rate of plus 50 per cent or over. In the case of the patients presenting evidence of liver damage no relation between the height of the metabolic rate and the degree of functional impairment of the liver was noted.

In Table 3 comparison is made between the basal metabolic rates and the test of liver function. The data in this table also have been studied statistically to determine further if any relation exists between metabolic rate and liver function. The average basal metabolic rate expressed in percentage of deviation from normal (tables of Aub and Dubois) is plus 57.1 per cent and the average liver function, expressed in per-

TABLE 3—*Comparison of Basal Metabolic Rate and Loss of Weight with Liver Function*^a

No	Case	Liver Function †	Basal Metabolic Rate (Maximum)‡ Deviation, per Cent	Loss of Weight (Kg)
1	5	0	50.5	11.3
2	8	0	24.6	10.0
3	9	0	35.5	
4	14	0	78.0	11.3
5	15	0	60.0	6.8
6	16	0	23.0	13.1
7	18	0	50.5	7.7
8	19	0	26.5	9.0
9	20	0	66.0	18.1
10	27	0	38.0	11.8
11	31	0	108.0	14.5
12	32	0	70.0	38.6
13	22	1	68.0	5.0
14	34	1	78.0	9.0
15	3	2	21.0	3.6
16	7	2	16.5	27.2
17	24	2	92.0	13.6
18	17	2.5	105.0	11.8
19	21	2.5	75.0	12.7
20	11	3	49.5	13.6
21	43	—3	91.0	10.0
22	44	—3	86.5	23.6
23	12	12 (15 min)	82.0	15.0
24	36	3	16.0	
25	25	3	61.0	13.6
26	29	3	21.0	9.0
27	37	3	25.0	
28	13	4	64.0	4.5
29	23	4	70.0	8.1
30	26	4	77.5	11.8
31	28	4	29.0	4.5
32	33	4	63.5	20.0
33	41	—5	56.0	4.5
34	2	5	36.0	9.0
35	10	5	39.5	31.8
36	35	5	54.0	4.0
37	38	5	73.5	7.2
38	39	5	44.0	7.2
39	1	5	45.7	2.7
40	42	5	72.5	4.5
41	6	8	70.0	
42	4	10	73.0	11.8
43	30	10	70.0	18.1
44	40	10	93.0	34.0

^a Table is arranged in the order of increasing degree of liver damage.

† Phenoltetrachlorophthalein method, percentage of dye retained at one hour.

‡ Percentage of deviation from normal, table of Aub and Dubois.

centage of dye retained at one hour, is 3.04 per cent. The standard deviation of the basal metabolic rate is 77.734 and of the liver function 2.814. The coefficient of correlation between basal metabolic rate and liver function is 0.2275 ± 0.0954 , thus substantiating the conclusions drawn above. Figure 2 is a scatter diagram similar to Figure 1 and illustrates well the lack of correlation between basal metabolic rate and liver function.

Loss of weight was a fairly constant factor in the patients showing liver damage, as might be expected in view of the nature of the disease. Frequently it was extreme and it amounted to 9 kg (20 pounds) or more in twenty-seven (67 per cent) of the forty patients in whom the loss of weight was determined. Table 3 gives a comparison between the loss of weight and the test of liver function. In an earlier article¹⁸ we stated that there was no constant relation between the loss of weight and the liver function. However, a statistical study of the data in Table 3 shows a slight correlation between these two factors. The

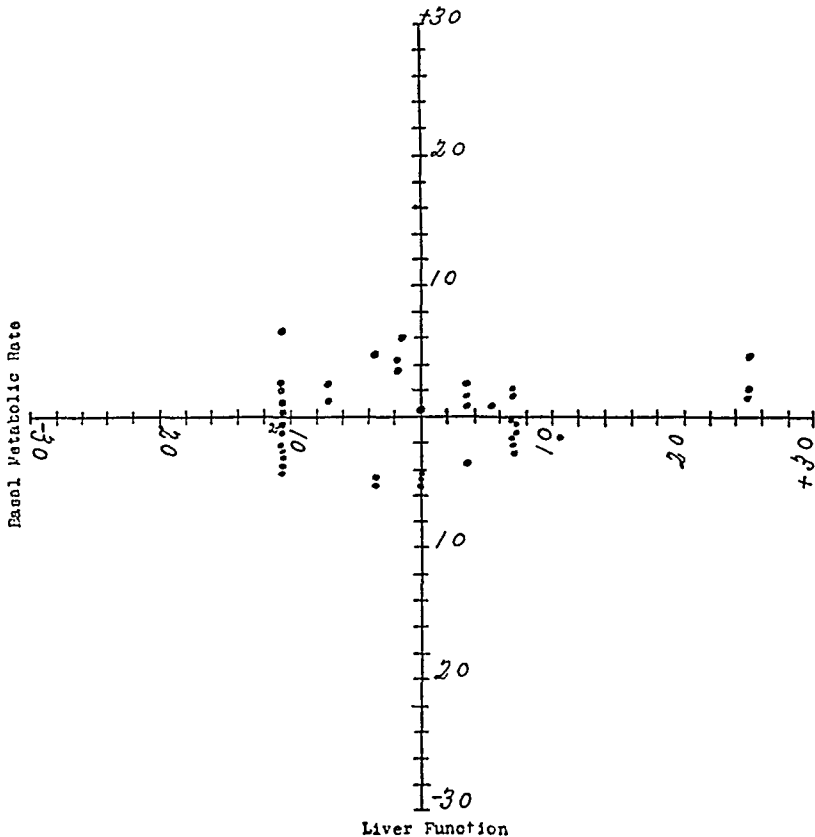


Fig. 2—Comparison between deviations from mean divided by standard deviation of basal metabolic rate, expressed as percentage of deviation from normal, and liver function, expressed as percentage of dye retained at one hour (from Table 3), Cases 11 and 12 have been omitted.

average loss of weight in kilograms is 12.5 and the average liver function expressed in percentage of the dye retained at one hour is 3 per cent. The standard deviation of the loss of weight is 8.419 and of the liver function 2.712. The coefficient of correlation between the loss of weight and liver function, thus expressed, is 0.4257 ± 0.0873 . Figure 3 is a scatter diagram similar to Figures 1 and 2 and illustrates this relation. It was noted clinically that evidence of liver injury was more

apt to be encountered in patients who, in addition to having lost weight, developed an inability to maintain a satisfactory caloric intake, a point that may be of some practical importance

Early in the course of this study it was thought that possibly some connection would be established between the liver injury and the clinical type of the disease. Further work showed the fallacy of such an assumption. Unfortunately, such attempted correlation is hampered by

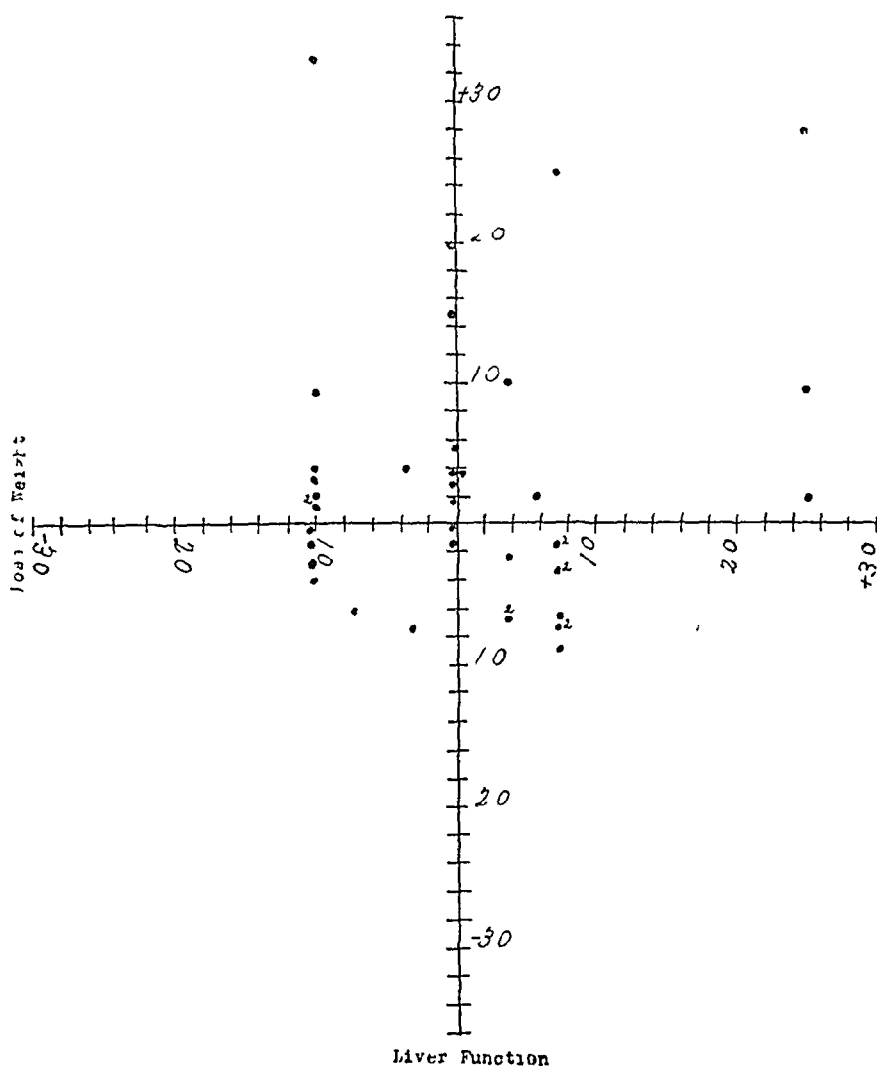


Fig 3—Comparison between deviations from mean divided by standard deviation of loss of weight in kilograms and liver function expressed in percentage of dye retained at one hour (from Table 3)

the lack of uniformity of classification or even of general agreement as to the exact etiology and pathology of the disease. In Table 1 it is seen that an attempt has been made to classify the various cases according to the clinical classification commonly used. Necessarily all the data used in making this classification cannot be given here. Comparison of various types so classified and the figures showing evidence of liver damage fail to show any definite association between any type of

the diseases and the presence or absence of injury to the liver. Neither was any relation apparent between the evidence pointing to liver damage and the acuteness or chronicity of the disease.

No relation between liver damage and such factors as age, sex or the usual laboratory examinations was noted, with one exception. Frank jaundice or a subicteric tint occurred in seven patients and in all but one instance occurred in the group of patients with the more severe liver damage, a fact consistent with the usual clinical interpretation of this finding.

The additional tests of liver function (levulose tolerance, hemoclastic crisis test and the determination of the concentration of bilirubin in the blood serum) were done in too few instances to warrant more than passing comment. The usual argument for the use of more than one test of the functional efficiency of the liver is based on the fact that many of these tests are tests of separate and distinct functions. It is assumed that one function might be impaired and the impairment detected without a disturbance of the other functions. We do not adhere strictly to this point of view, but it is entirely possible that the tests vary in their sensitiveness and that one of the tests might give evidence of an impaired function in spite of negative results with the other tests.

The data obtained by the various tests of liver function are shown in Table 4. In general it might be said that the levulose tolerance test failed to give evidence of impairment of liver function when present as often as did the phenoltetrachlorphthalein test. Once both were negative, and once the levulose tolerance test was positive and the phenoltetrachlorphthalein test negative. Since, as stated above, the technic of the hemoclastic crisis test used by us differs from that described by the originators, comparison between it and other methods is not warranted.

Early in this work it was noted that the serum of the blood samples following the injections of the phenoltetrachlorphthalein showed an apparent increase in the bilirubin content, an observation also made by Blum and Rosenau.⁶ Later it was noted that the blood drawn previous to the injection of the dye frequently showed a similar change. We concluded that some of these patients had an increase in the serum bilirubin independent of any increase possibly due to the dye. It was therefore determined to test the amount of bilirubin in the blood serum of these patients, using for this purpose blood secured before the injection of the phenoltetrachlorphthalein. This test was made in twelve cases. The bilirubin was found increased seven times and in six of the seven cases the phenoltetrachlorphthalein test was positive. Twice it was found in normal amounts, both times associated with a negative phenoltetrachlorphthalein test. In three cases the test was unsatisfactory. These results are not surprising since jaundice occurred in three

cases and a subicteric tint was noted in four additional cases. Since icterus occurred it might be expected that this test, which reveals latent jaundice, would frequently be positive. These findings, we believe, offer strong additional evidence of the considerable frequency of liver damage in the cases studied since an increase in the bilirubin content of the blood serum seems to be fairly constant in cases of liver injury.¹⁵

An increased functional efficiency of the liver has been noted in certain stages of some diseases.¹⁹ Usually in such cases later evidence of injury and a decreased function occur, suggesting that the first reaction of the liver to insult may be increase in its activity. An increased functional activity is difficult to detect with the tests of liver function used but it was thought that the finding of an unusually low percentage of the dye in the blood stream at the fifteen minute period, as was sometimes encountered, might be evidence of an increased function in some cases.

COMMENT

The foregoing analysis of the results would seem to warrant certain tentative conclusions. In the first place, no causal relation between liver injury and the decreased glucose tolerance of thyrotoxicosis seems to have been demonstrated. It might be argued that the glucose tolerance is itself a test of liver function and that its decrease indicates an impairment of the function of that organ. This view seems scarcely tenable to us in view of the many other factors that might affect the glucose tolerance in this disease and the absence of data in other conditions indicating such a close relation between glucose tolerance and liver function. However, although our findings fail to disclose evidence of a causal relation between liver damage and the decreased glucose tolerance in thyrotoxicosis, there is, we believe, a very definite relation between the liver damage and the disturbed carbohydrate metabolism present in this disease. A glycogen poor liver has frequently been shown experimentally in such conditions as phosphorus and chloroform poisoning to possess an increased susceptibility to injury. It has also been shown²⁰ that the feeding of thyroid substance or extract to animals not only causes a loss of glycogen from the liver but prevents the storage of glycogen in that organ. In addition, spontaneous glycosurias have been observed in patients treated with thyroid preparations and may indicate a disturbance in glucose tolerance similar to that occurring in thyrotoxic states. It is probable, therefore, that a change in thyroid activity in thyrotoxicosis may result in a glycogen free or poor liver,

19 Chirav, M. L'acide Glycuronique Urinaire, Sa Valeur pour le Diagnostic de L'insuffisance Hepatique, *Paris med* **31** 359 (May 3) 1919.

20 Kuriyama S. The Influence of Thyroid Feeding upon Carbohydrate Metabolism I, The Storage and Mobilization of the Liver Glycogen in Thyroid Fed Animals, *J Biol Chem* **33** 193 (Jan) 1918.

more susceptible to damage by some toxic agent present in this disease or more susceptible to injury by the disturbed thyroid function itself. Not, indeed, if one may be permitted to speculate, need the conceptions of such a process be limited to the liver alone. The possible effect of such a toxic action on organs made poor in glycogen, such as the heart, at once becomes apparent. Added support is given to such an hypothesis by the well known beneficial effects of glucose in this disease.

In an attempt to throw further light on these problems we have performed some preliminary experiments in which dogs were fed thyroid extract and the effect of such feeding on liver function determined by the use of the phenoltetrachlorophthalein test. So far the results indicate that neither the feeding of large amounts over short periods of time or the feeding of small amounts over a longer period has any effect on the functional efficiency of the liver. Further work on this phase of the problem has been planned.

Practically, the significance of injury to an organ so important and of such varied functions as the liver is obvious. Further study may indicate which of, and to what extent, its various functions are involved and the relation of such injury to prognosis and therapy. Of still greater importance is the possible effect of a disturbed carbohydrate metabolism in connection with the injury to a number of important tissues and organs.

CONCLUSIONS

1 Tests of liver function have been made in forty-four patients with thyrotoxicosis. In twenty-eight of the patients tests of the glucose tolerance also were made.

2 Twenty-two, or 50 per cent, of the patients in this series showed an impairment of liver function according to the tests of liver function used. Twenty-one of the twenty-seven cases satisfactorily tested showed a decreased glucose tolerance.

3 No relation was found to exist between the functional efficiency of the liver as tested and the glucose tolerance, basal metabolic rate or other features of the disease except loss of weight.

4 The impairment of liver function in thyrotoxicosis seems to be associated to some degree with loss of weight.

HYPERGLYCEMIA

II PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD FROM CASES OF DIABETES MELLITUS *

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In a previous article ¹ I have discussed the relation of hyperglycemia to variation in the water content of the blood and of the body tissues. It was observed that all young diabetic patients responded to hyperglycemia by a concentration of the blood and an exsiccation of the tissues, while in arteriosclerotic diabetic patients the response was simply a dilution of the blood with little or no tissue dehydration. It emphasizes the precarious condition of the young diabetic patient, for he is not only liable to acidosis and coma as a result of deranged fat metabolism but also, because of the nonvolatile acidosis that accompanies anhydremia, he is continually suffering some diminution of the alkaline reserve of his blood plasma. Thus the young diabetic patient is always potentially in a state of acidosis. On the other hand, in the absence of factors that cause acute exacerbation, the arteriosclerotic diabetic patient is not afflicted with a nonvolatile acidosis and, for other reasons previously mentioned, does not so readily or so frequently fall a victim to diabetic coma. In the event of an acute exacerbation the arteriosclerotic diabetic patient becomes exsiccated and otherwise behaves exactly as a young diabetic patient.

In view of the fact that large differences were found in the water content of the bloods of these patients, a difference in the two large groups mentioned above and differences in the blood of any given case due to the administration of insulin, it was hoped that further means of differentiation might be afforded by a study of some of the physical and chemical properties of the blood and blood serum in serial samples taken from patients in both groups.

METHOD

The following determinations were made on each sample. Specific conductivity at 5 degrees C of the whole blood and of the serum, chlorin in the whole blood and in the serum, glucose in the whole blood and in the serum, erythrocyte counts, and in certain instances

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¹ Foshay Lee Hyperglycemia, I, The Relative Blood Volumes in Diabetes Mellitus, Arch Int Med 36 889 (Dec) 1925

the plasma carbon dioxide combining power From the foregoing data the following were calculated the relative volumes of serum and cells, the volume of the average erythrocyte, glucose content of the erythrocytes and chlorin content of the erythrocytes

1 *Preparation of Samples*—Blood was drawn from an antecubital vein with the utmost care to avoid venous stasis for more than a brief moment Part of this blood was immediately oxalated for the determination of whole blood glucose and chlorin The remainder was carefully defibrinated in chemically clean porcelain dishes by means of thin wooden applicator sticks By this method visible hemolysis was rare Whenever gross hemolysis occurred, the sample was discarded

2 *Erythrocyte Counts*—These were made in duplicate with the same pipet and counting chamber All counts that did not check within 250 000 per cubic millimeter were discarded In each instance the figure given represents the average of the two counts made on the defibrinated blood

3 *Electrical Conductivity*—The apparatus consisted of a combined resistance box and Wheatstone bridge furnished by the Central Scientific Company, bright platinum electrodes, a variable temperature water-bath, a simple induction coil operating on dry cells, a microphone and several U tubes The conductivity cells required about 3 c c of blood or serum The cell constants were determined repeatedly throughout the course of the work by means of a standard fiftieth molar potassium chlorid solution All determinations were made at temperatures somewhere between 5 and 10 degrees C Temperature correction to 5 degrees C was made in every instance by means of previously constructed tables showing the thermal coefficient of conductivity of blood serums containing various chlorin concentrations at temperatures from 0 to 30 degrees C These tables are accurate to 0.1 degree C For practical purposes one such table was found to be sufficient, since within the range of temperatures employed the maximal variation in chlorin concentrations caused a difference of only $0.2 \text{ K} \times 10^4$ per degree Centigrade The same conductivity cell was always used to determine the conductivity of the whole blood and of the serum from each blood sample After measuring the conductivity of the whole blood, the specimen was centrifugated and the procedure repeated on the serum The results are expressed as specific conductivities, that is, $\text{K} \times 10^4$ at 5 degrees C

4 *Relative Volumes of Serum and Erythrocytes*—These were calculated from the conductivity measurements by means of the relation developed by Stewart²

2 Stewart, G. N. The Relative Volume or Weight of Corpuscles and Plasma in Blood, *J. Physiol.* **24** 356 (July) 1899

5 *Average Erythrocyte Volume*—The relative volume of erythrocytes in cubic millimeters divided by the number of erythrocytes per cubic millimeter gives the volume occupied by the average erythrocyte. The results are expressed as cubic microns.

6 *Glucose*—This was determined both in the whole blood and in the serum by the method of Folin and Wu.³

7 *Chlorin*—This was determined by Whitehorn's method.⁴

8 *Corpuscular Chlorin and Corpuscular Glucose Concentrations*—These were calculated from the foregoing data according to the formula

$$\% \text{ in cells} = \frac{\% \text{ in whole blood} - (\text{serum volume } \% \times \% \text{ in serum})}{\text{Cell volume } \%}$$

9 *Grams Glucose and Grams Chlorin per Erythrocyte*—Calculated from the respective concentrations, relative volume of erythrocytes and erythrocyte counts from the formula

$$\frac{\text{Grams substance per 1 cu. mm. cells} \times \text{cell volume } \%}{\text{Number of cells per cu. mm.}} = \text{Grams substance per cell}$$

ELECTRICAL CONDUCTIVITY

A study of the electrical conductivity of the whole blood and serum has led to little that is new. The conductivity of whole blood varies inversely as the concentration. It thus provides a fairly good indication of changes in blood viscosity in serial samples. The ratio of the conductivity of the serum to the conductivity of the blood ($\frac{K_s}{K_b}$) is an index of changes in blood viscosity due entirely to increase or decrease in the number and size of the erythrocytes, particularly in serial samples of blood, since any change in the fluidity of the serum is absorbed in the ratio. Ordinarily there is a consistent relationship between the chlorin concentration and the conductivity of the serum. A serum containing 0.5 per cent chlorin usually has a conductance of about 72×10^{-4} , and a sample containing 0.64 per cent chlorin usually one of about 77×10^{-4} . In Cases 15 and 22 there are conductivities that are considerably higher than the respective chlorin concentrations might lead one to expect. Indeed, in Case 15 the serum conductivities are much higher than the conductivities of equivalent concentrations of sodium chlorid in pure water (Fig. 3). This discrepancy is the same whether the relative volume of serum is above or below the normal.

This phenomenon has been described before in cases of salt and water retention nephritis and is called the "conductivity chlorid discrep-

³ Folin, O., and Wu, H. System of Blood Analysis, J. Biol. Chem. 38:81 (May) 1919.

⁴ Whitehorn, J. C. System of Blood Analysis, J. Biol. Chem. 45:449 (Feb.) 1921.

ancy”⁵ It is mentioned here to record a similar occurrence in the blood in diabetes The cause of this discrepancy is not clear It has been thought that a diminished protein concentration in the serum might account for it,⁶ since in solutions containing salts that are highly ionized the conductance curves parallel the fluidity curves However

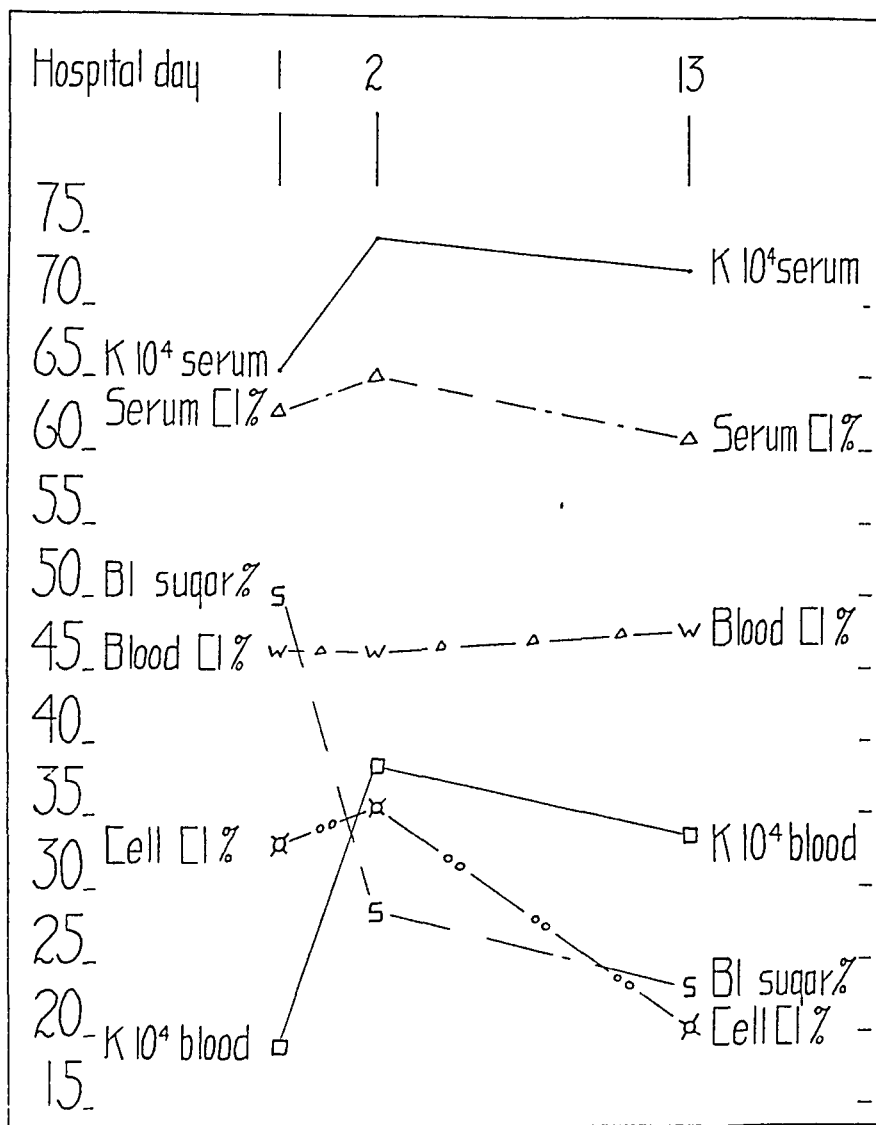


Fig 1 (Case 33) —Blood and serum conductivities and chlorin concentrations from a case of diabetic coma, showing the changes that follow insulin administration, transient type of conductivity chlorin discrepancy present only on first day

5 Atchley, D W , Loeb, R F , Benedict, E M , and Palmer, W W Physical and Chemical Studies of Human Blood Serum, Arch Int Med **31** 606 (April) 1923

6 Bugarsky, S, and Tangl, F Physikalisch-chemische Untersuchungen über die molekularen Concentrationverhältnisse des Blutserums, Arch f d ges Physiol **72** 531 (Sept) 1898 Palmer, W W , Atchley, D W , and Loeb, R F Studies in Regulation of Osmotic Pressure, Effect of Increasing Concentrations of Albumin on Conductivity of a Sodium Chlorid Solution, J Gen Physiol **3** 801 (July) 1921, ibid **4** 585 (May) 1922

observed values have been recorded which indicate that this is not the completed explanation⁵

In two other instances, in Cases 33 and 35, there was noted a conductivity chlorid discrepancy of the opposite nature, that is a serum conductance much lower than the chlorin concentration would lead one to expect, but this was a transient effect in each instance, and its dis-

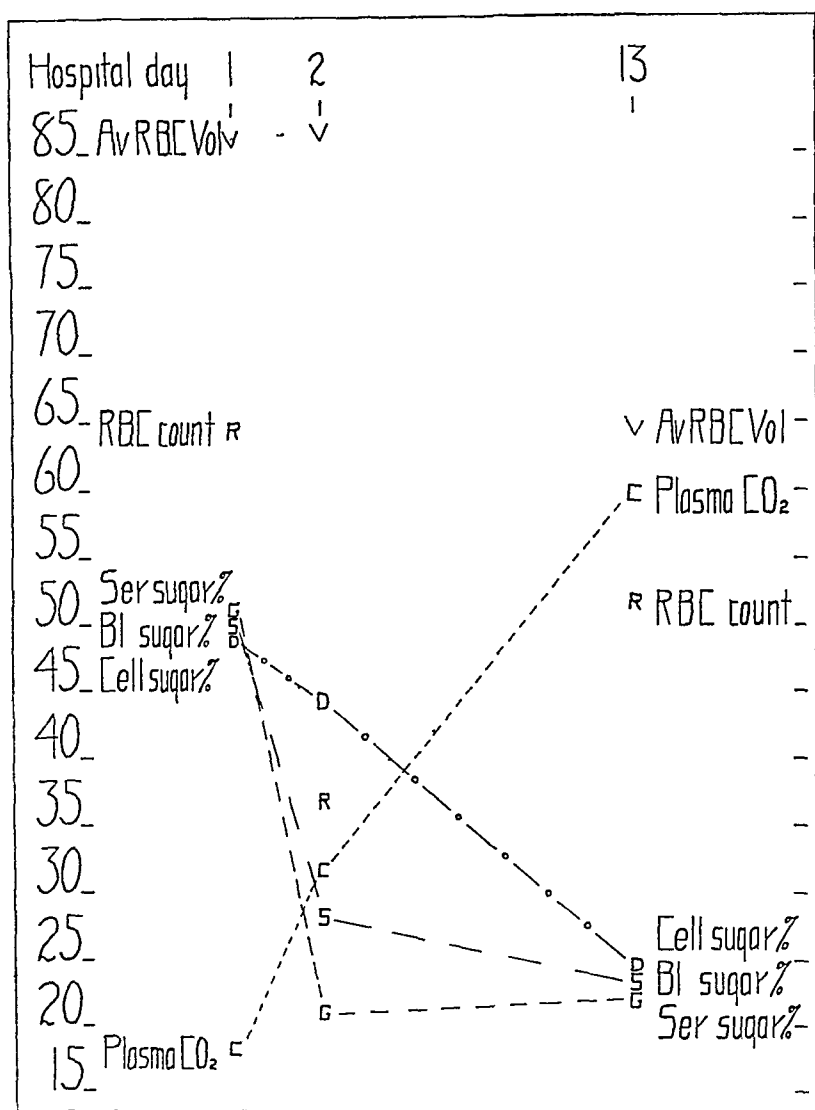


Fig 2 (Case 33)—Average erythrocyte volume, erythrocytes per cubic millimeter, plasma carbon dioxide and glucose distribution during diabetic coma and the changes that follow insulin treatment, lag in diffusion of glucose from cells to serum as blood sugar is being reduced (Figures 1 and 2 are from the same case as Figure 1 in Part I of the series)

appearance after the relative blood volumes were restored to normal indicates that in this type of discrepancy the depression of the conductivity was actually a function of the fluidity of the solvent (Fig 1) Many observers have shown that the addition of a nonelectrolyte to an

electrolytic solution will depress the conductivity⁷ Javal and Boyet⁸ state that urea will not do so when added to blood serum This appears to be true in Case 34, in which the urea concentrations were high

WATER TRANSFERENCE BETWEEN SERUM AND ERYTHROCYTES

The normal volume of the average erythrocyte has been found to be approximately 76 cubic microns This was determined from the bloods of thirteen normal subjects in the resting state by means of erythrocyte counts and the relative volume of cells measured by the electrical method As the standard deviation of this series was $3.4\mu^3$ with a probable error of $\pm 2.3\mu^3$, it was not deemed necessary to examine a larger number of blood samples

From the data in Table 1 it is seen that, at the time of admission to the hospital, all young diabetic patients and two of the arteriosclerotic diabetic patients with acute exacerbations (Cases 14 and 21) had very large erythrocytes, averaging from 85 to 90 cubic microns If the patient died the volume remained stationary at subsequent examinations, but with recovery of the patient the size of the erythrocytes returned to normal With the exception of the two patients mentioned above, one of whom died, all of the arteriosclerotic diabetic patients behaved differently, even in the presence of acute exacerbations of symptoms In these patients there was no increase in the erythrocyte volume even in the presence of hyperglycemia up to 0.53 per cent (Cases 1, 10, 13, 15, 22 and 26)

Thus, in comparing these two groups of diabetic patients, those without and those with advanced arteriosclerosis, there is a marked disparity in the manner in which the erythrocytes respond to the changes induced by hyperglycemia In the patients of the first group the erythrocytes imbibe water and increase their volume, while in those of the second group there is apparently no water transference

Persistent macrocytosis or microcytosis has been described as a characteristic feature of a wide variety of diseases Probably the macrocytosis of pernicious anemia and the microcytosis of chronic posthemorrhagic secondary anemia are the best known examples Transient changes in the size of the erythrocyte are not characteristic of any disease entity but have been observed only when the blood p_H or the alkaline reserve of the plasma has been altered either by natural process, by morbid process or by experimentation Thus Price-Jones⁹ observed the diurnal variation in the size of the erythrocyte in normal

⁷ Kraus, C. A. The Properties of Electrical Conducting Systems, New York, 1922, p. 121

⁸ Javal and Boyet. Variations de la Conductibilité électrique du Serum Sanguin, Compt rend Soc de biol **68** 442 (March) 1910

⁹ Price-Jones, C. The Diurnal Variations in the Size of the Red Blood Cells, J Path & Bacteriol **23** 371 (Dec.) 1920

TABLE 1—Physical and Chemical Determinations on Blood from Diabetic Patients

Case	Date	$k \times 10^4$ at 5 C		Per Cent by Volume		Glucose			Chloim			Red Blood Cells per Cmm, Millions	Volume of Average Red Blood Cells, Cubic Microns	Plasma Carbon Dioxid, per Cent by Volume
		Blood	Serum	Serum	Cells	Blood, per Cent	Serum, per Cent	Cells, per Cent	Blood, per Cent	Serum, per Cent	Cells, per Cent			
1	11/23/23	34.4	71.5	64.4	35.6	0.53			0.420	0.580	0.130	4 700	75.8	42.0
	11/26/23	41.2	77.2	70.9	39.1	0.15								50.0
	12/19/23	43.7	79.1	72.0	28.0	0.11								
10	1/30/24	30.6	70.8	57.1	42.9	0.33						3 800	73.7	
	3/10/24	31.7	78.8	57.2	42.8	0.18						5 595	76.7	
										0.643	0.676	5 700	75.1	
13	4/18/24	32.6	77.7	60.8	39.2	0.30				0.627		4 995	78.5	
	1/22/24	31.7	76.2	59.2	40.8	0.27				0.610		6 195	65.9	
	4/20/24	33.0	77.0	62.0	38.0	0.17				0.593		5 090	74.7	
14	5/10/24	29.3	77.9	54.4	45.6	0.26				0.627		5 920	77.1	
15	1/20/24	26.6	71.9	54.5	45.5	0.35			0.460	0.594	0.299	5 330	85.8	16.1
	4/21/24	24.5	76.9	62.6	37.4					0.659		4 215	88.8	12.5
	1/22/24	28.6	74.3	55.9	44.1	0.60				0.651		5 355	82.4	
17	5/7/24	21.6	73.5	41.7	55.3	0.40			0.300	0.528	0.155	7 350	75.3	58.0
	5/7/24	31.0	80.1	55.5	44.5	0.17				0.594		5 810	76.6	
	5/10/24	31.9	77.2	58.7	41.3	0.16				0.761		5 570	74.2	
20	5/14/24	32.4	80.0	57.1	42.6	0.17				0.709		5 120	83.2	
	5/19/24	30.0	76.1	56.8	43.2	0.24				0.577		5 700	75.7	
	5/23/24	37.0	81.4	63.8	36.2	0.17				0.551		5 920	61.1	
21	5/23/24	26.5	73.0	53.6	46.4	0.43			0.370	0.561	0.106	5 850	86.7	46.6
22	5/30/24	23.9	73.9	48.6	51.4	0.37			0.350	0.610	0.105	6 420	80.1	
	6/11/24	26.3	73.2	52.5	47.5	0.20			0.360	0.592	0.104	5 450	87.3	
	6/18/24	28.3	71.8	55.1	44.9	0.18			0.447	0.627	0.226	5 970	75.2	
23	6/8/24	37.5	80.5	63.6	36.4	0.07			0.400	0.577	0.338	5 440	66.9	
	6/13/24	36.9	75.6	67.0	33.0	0.15			0.478	0.660	0.109	4 670	70.7	
	6/17/24	33.0	76.1	61.1	38.9	0.21			0.405	0.660	0.236	4 980	78.1	
23	6/8/24	30.7	76.1	57.9	42.1	0.20			0.370	0.599	0.055	4 800	87.7	
	6/13/24	33.4	73.2	64.2	35.8	0.18			0.462	0.643	0.137	3 900	89.1	
	6/17/24	33.5	73.2	64.2	35.8	0.38			0.478	0.594	0.240	4 300	83.1	

24	6/10/24 6/17/24	30.7 32.2	72.2 73.5	60.9 62.0	39.1 38.0	0.14 0.12				0.400 0.447	0.774 0.627	0.252 0.153	0.164 0.110	6.730 5.450	58.1 69.7
25	6/10/24 6/18/24	32.3 33.2	74.8 74.8	61.1 62.5	38.9 37.5	0.13 0.16				0.410 0.493	0.595 0.627	0.197 0.275	0.124 0.205	6.170 5.020	63.1 74.7
26	6/10/24 6/17/24	29.5 27.5	74.8 71.5	57.0 36.3	43.0 43.7	0.17 0.22				0.440 0.420	0.620 0.447	0.202 0.198	0.129 0.143	6.740 6.080	63.9 72.0
28	6/10/24 6/17/24	30.0 32.7	74.5 74.5	58.0 62.0	42.0 38.0	0.24 0.22				0.460 0.412	0.641 0.643	0.210 0.025	0.169 0.020	5.210 4.840	80.7 78.5
29	6/10/24 6/17/24	31.4 33.2	74.5 74.9	60.2 62.4	39.8 37.6	0.16 0.14				0.491 0.495	0.598 0.660	0.327 0.221	0.251 0.171	5.190 4.840	76.7 77.6
30	6/11/24 6/18/24	29.4 28.9	72.2 72.2	58.9 58.8	41.1 41.2	0.26 0.24				0.360 0.447	0.560 0.643	0.074 0.168	0.057 0.147	5.360 4.720	76.8 87.4
33	9/11/24 9/12/24 9/23/24	19.3 37.8 34.8	66.7 74.0 72.5	44.7 69.5 66.8	55.3 30.5 33.2	0.50 0.28 0.23	0.499 0.439 0.250	0.428 0.378 0.148		0.462 0.462 0.478	0.626 0.649 0.610	0.330 0.360 0.212	0.283 0.310 0.136	6.450 3.545 5.155	85.8 86.1 64.4
34	9/23/24 9/26/24	50.6 48.5	72.8* 70.8†	84.8 86.0	15.2 14.0	0.08 0.38	0.246 0.686	0.153 0.337		0.528 0.577	0.610 0.627	0.072 0.270	0.045 0.133	2.445 2.835	62.3 49.1
35	7/ 5/24 7/ 7/24 7/10/24 7/13/24	14.5 20.5 34.9 38.2	60.8 63.1 71.1 75.0	38.2 49.8 63.3 69.1	61.8 50.2 31.7 30.9	0.15 0.13 0.09 0.07	0.138 0.140 0.076 0.030	0.116 0.123 0.053 0.017		0.505 0.340 0.478 0.495	0.700 0.503 0.633 0.660	0.385 0.218 0.144 0.125	0.824 0.192 0.100 0.071	7.230 5.700 4.570 5.450	84.2 88.1 69.4 56.6
36	11/20/24	21.1	76.6	42.2	37.8	0.38	0.35	0.277		0.400	0.640	0.225	0.178	7.310	79.1
37	11/26/24	28.8 28.9 27.9	77.1 76.7 75.4	54.2 54.7 54.2	45.8 45.3 45.8	0.21 0.23 0.21	0.198 0.205 0.257	0.147 0.167 0.205		0.428 0.412	0.652 0.627	0.163 0.192 0.158	0.122 0.156 0.122	6.160 5.560 5.740	74.4 81.5 79.8
38	12/ 4/24	29.4 32.6 29.6 29.9	73.6 75.0 72.8 74.7	57.7 61.4 58.8 56.4	42.3 38.6 41.2 43.6	0.25 0.25 0.30 0.23	0.22 0.20 0.84 0.23	0.179 0.135 0.269 0.169		0.462 0.462 0.462 0.462	0.611 0.640 0.611 0.528	0.259 0.179 0.129 0.377	0.210 0.121 0.102 0.276	5.210 5.710 5.220 5.950	81.2 87.6 79.0 73.3
39	2/ 4/25	30.0 29.5 28.6 29.2	71.4 70.9 70.0 71.4	60.5 60.1 59.6 59.4	39.5 39.9 40.4 40.6	0.27 0.26 0.21 0.23	0.26 0.22 0.136 0.240	0.207 0.190 0.108 0.217		0.460 0.460 0.478 0.478	0.627 0.601 0.594 0.626	0.205 0.248 0.307 0.261	0.164 0.214 0.264 0.236	4.055 4.630 4.700 4.485	79.8 86.2 85.9 90.5

* Blood urea, 224 mg per hundred cubic centimeters
† Blood urea, 187 mg per hundred cubic centimeters

men and correlated the changes in size with variation in the reaction of the blood. Dautrebande and Davies¹⁰ noted an increase in erythrocyte volume following violent exercise. I have repeatedly found erythrocytes with volumes ranging from 90 to 97 cubic microns in cases of nephritic acidosis and in lobar pneumonia, and many observers have found experimentally that adding carbon dioxide, lactic acid, hydrochloric acid and other acids to blood causes an increase in the volume of the erythrocytes.

Mellanby and Wood,¹¹ working with carbon dioxide on sheep's blood, have shown that this reaction is reversible. If blood saturated with carbon dioxide and containing swollen erythrocytes is allowed to stand for a period of hours, the volume of the erythrocytes gradually diminishes and eventually returns to normal. Now, in the young diabetic patient, if this increase in volume is due wholly to increased carbon dioxide tension, it seems remarkable that such large erythrocytes should ever be found in samples of defibrinated blood, since the process of defibrination would be expected to facilitate greatly the reversal of the reaction. Yet Case 33 shows an increase in volume 33 per cent greater than the volume finally obtained, and Case 35 shows an increase of 55 per cent. These observations were made on defibrinated blood. In the former case it is possible that carbon dioxide, the ketone acids, lactic acid and other ether-insoluble acids, such as oxyproteic acid, have combined to cause the water transfer. Whatever may be the cause of the decrease in the p_H of the blood, it seems probable that acids other than carbon dioxide are operative in producing this effect. In the latter case, which was not diabetic but a case of extreme excitation and temporary anuria resulting from the persistent vomiting and diarrhea of acute food poisoning, the diminished p_H was probably due not only to abnormal organic acids but also, because of the anuria, to retained inorganic acids. This case is included in the table because in all respects, the glucose concentration excepted, it is identical with Case 33, a case of typical diabetic coma.

It is interesting to note that even with a marked change in corpuscular volume there may be no change at all in the corpuscular chlorine concentration. This is in accord with the observations of Van Slyke, Wu and McLean¹² who found that the reaction occurs regardless of the chlorine shift, which apparently has nothing to do with the total osmotic changes.

10 Dautrebande, L., and Davies, H. C. A Study of the Chlorine Interchange Between Corpuscles and Plasma, *J. Physiol.* **57** 36 (Dec.) 1922.

11 Mellanby, J., and Wood, C. C. The Influence of Carbon Dioxide on the Interchange of Ions Between the Corpuscles and the Serum of Blood, *J. Physiol.* **57** 113 (March) 1923.

12 Van Slyke, D. D., Wu, H., and McLean, F. C. Studies of Gas and Electrolyte Equilibria in the Blood, V, Factors Controlling the Electrolyte and Water Distribution in the Blood, *J. Biol. Chem.* **56** 765 (July) 1923.

Table 2 shows the average erythrocyte volume, the average number of erythrocytes and the average relative volume of erythrocytes found in this series of diabetic patients. The same data from normal adult males are included for comparison.

To summarize, the order of events in diabetes would seem to be somewhat as follows. In young patients hyperglycemia produces a dehydration of the blood and of the fixed tissues, thus causing a non-volatile acidosis with consequent increase in erythrocyte volume by reason of water transference. This may be considered the predisposing cause of diabetic acidosis. As cellular metabolism becomes more and more abnormal there is a production of ketone acids in increasingly larger amounts, this further diminishes the plasma alkaline reserve. This might be called the exciting cause of diabetic acidosis. In cases of severe acidosis with rapid onset, no doubt both processes become important factors.

In elderly, arteriosclerotic patients, hyperglycemia does not result in dehydration and acidosis, hence no water transference from the

TABLE 2—*Averages of Relative Volumes, Numbers and Sizes of Erythrocytes in this Series of Patients*

	Average Red Blood Cells, Volume in Cubic Microns	Average Red Blood Cells, per C Mm Millions	Average Rela- tive Volume of Cells, per Cent
Young diabetic patients	84.0	5.700	47.8
Arteriosclerotic diabetic patients	73.6	5.300	39.0
All diabetic patients after establishment of constant relative blood volumes	73.0	5.200	38.0
Normal adult males	76.0	5.470	41.6

plasma to the erythrocytes and no increase in erythrocyte volume occurs. The patients live in relative comfort and are not in constant danger of acidosis and coma. If a serious dietary indiscretion or acute infection supervenes, then dehydration, acidosis and coma occur just as in the young diabetic patient.

DISTRIBUTION OF GLUCOSE BETWEEN SERUM AND ERYTHROCYTES

There has been much controversy over the question whether glucose is present within the erythrocyte or not. The conclusive experiments of Ege, Gottlieb and Rakestrow¹³ leave little doubt as to its presence in variable quantities, depending entirely on the glucose concentration in the plasma (Fig. 2).

In a number of cases the corpuscular glucose was determined both directly and by calculation. Changes in the concentration measured by

¹³ Ege, R., Gottlieb, E., and Rakestrow, N. The Distribution of Glucose Between Human Blood Plasma and Red Corpuscles and the Rapidity of Its Penetration, *Am J Physiol* **72**: 76 (March) 1925.

the two methods were always homodirectional in successive samples, but the figure obtained by the direct method was always too high because of the impossibility of obtaining the cells entirely free from serum. This made it impossible to check the figures against the blood

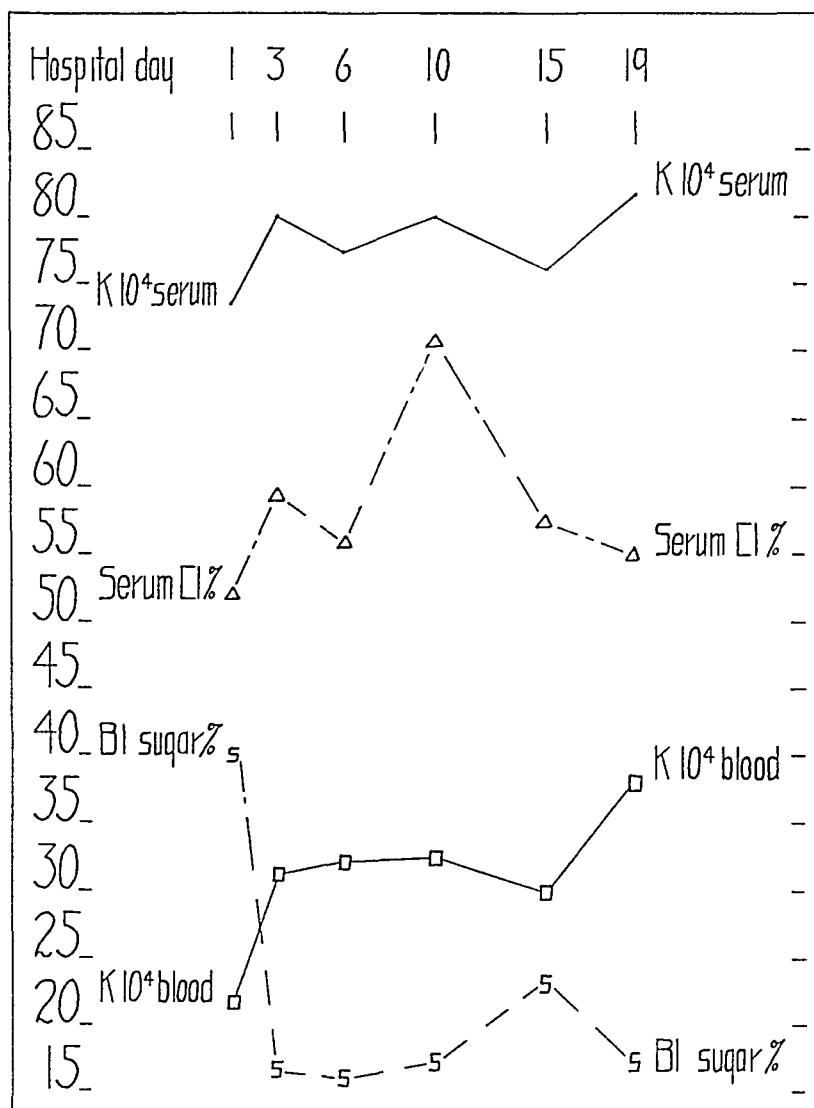


Fig 3 (Case 15) —Blood and serum conductivities, serum chlorin concentration and blood sugar from case of diabetic coma, persistence of conductivity chlorid discrepancy (The data are from the same case as Figure 2 in Part I of this series)

and serum sugars so that the method was discarded in favor of the more accurate calculation

In general the corpuscular glucose is usually a little less than the concentration in the serum. However, as previously found in dogs,¹⁴

¹⁴ Foshay, Lee. Observations Upon the Action of Insulin on the Blood, with Special Reference to the Cause of the Condition Known as Hypoglycemia, *Am J Physiol* 73 470 (July) 1925

with a steadily increasing hyperglycemia, by far the greater portion of the glucose is found in the serum and, conversely, with a steadily diminishing glycemia the major portion of the glucose is in the cells. The diffusion lag seems to be shorter in duration than it is in the dog.

Occasionally, if the transfer of water from the serum to the erythrocytes, or vice versa, has been large, the figures for corpuscular glucose concentration become somewhat misleading. For instance in Case 34 the corpuscular glucose concentration increased from 0.246 to 0.686 per cent, almost a threefold increase, whereas the actual quantity of glucose increased from 0.153 to 0.337×10^{12} gm, a little more than a twofold increase. The discrepancy is due to the diminution in the volume of the erythrocytes as a result of water loss. Again, in Case 39 in the first sample the corpuscular glucose concentration is 0.26 per cent and falls to 0.24 per cent in the fourth sample. As a matter of fact the quantity of corpuscular glucose had risen from 0.207 to 0.217×10^{12} gm. Here the apparent decrease in concentration is really only a dilution of a larger amount of glucose by means of water imbibition.

The characteristic effect of insulin on the distribution of glucose between serum and erythrocytes is well shown by a comparison of the glucose concentration of the blood, serum and cells in Case 39. This remarkable effect has been studied and reported elsewhere¹⁴

THE CONCENTRATION OF CHLORIN IN THE BLOOD AND IN THE SERUM, AND THE DISTRIBUTION OF CHLORIN BETWEEN SERUM AND ERYTHROCYTES

Normally the concentration of chlorin is about 0.48 per cent in the blood, 0.61 per cent in the serum, and from 0.3 to 0.31 per cent in the erythrocytes¹⁵. These are subject to extremely wide variations even in health. The only constant finding in diabetes is that in the presence of hyperglycemia the chlorin concentration in the whole blood is always diminished, averaging 0.37 per cent in the initial samples of blood from severe cases. This loss of chlorin is not borne equally by the serum and the erythrocytes. In most cases the greater reduction occurs in the cells. However, in the severest cases of diabetic coma the corpuscular chlorin is either within normal limits or definitely increased, as in Cases 14, 33 and 36.

If whole blood is subjected to an increasing carbon dioxide tension, or if certain other acids are added, there is a transference of chlorin from the serum into the erythrocytes. Despite osmotic inequality on the two sides of the cell membrane, the chlorin is held in the cells by

¹⁵ Norgaard, A., and Gram, H. C. The Relation Between the Chloride Content of the Blood and Its Volume Per Cent of Cells, *J. Biol. Chem.* **49** 263 (Dec.) 1921

virtue of the restraint imposed on the membrane by the nondiffusible cations, chiefly Na^+ and K^+ ¹⁶

Dautrebande and Davies ¹⁰ found that in vitro it was necessary to add sufficient acid to neutralize all the blood bicarbonate before there was any appreciable chlorin transfer. They point out, however, that with an acidosis in vivo it is obvious that reduction of the bicarbonate reserve would cause transference to occur more readily when the blood becomes venous, because under such conditions the available alkali combined with proteins is diminished. Thus on *a priori* grounds one would expect to find a material increase in corpuscular chlorin only in the severe cases of diabetic acidosis.

A consistent relationship between hyperglycemia and corpuscular chlorin has not been found, although the results in Cases 23, 24, 29, 33 and 34 suggest the possibility. If so, this appears to offer further support to the idea that in young diabetic patients the blood alkalinity varies inversely as the glucose concentration. The failure to obtain a consistent relationship may be due to the fact that all of these patients were treated with insulin, which causes rapid changes to occur in the distribution of glucose, chlorin and water. In hyperglycemic dogs the corpuscular chlorin concentrations parallel the blood sugar curves, but after insulin has been given the comparative results are very irregular ¹⁷. So in patients the relative concentrations found in any sample of blood depend largely on the conditions that existed prior to the administration of insulin and on the interval of time that may have elapsed between the injection of insulin and the collection of the blood. When serial specimens are collected carefully with the same time interval after insulin and food, as in Case 33, then the diminution in the relative volume of serum, depression of the specific conductivity of the serum, increase in the corpuscular volume, increased corpuscular glucose and chlorin, and diminished alkaline reserve all show simultaneous reversals as a result of the action of insulin (Figs 1 and 2).

The same discrepancy is noted between the chlorin concentration in the erythrocytes and the actual amounts of chlorin per erythrocyte as was previously described for glucose. The reason for the discrepancies is the same, namely, the transference of water between the serum and the erythrocytes.

SUMMARY

In the two types of "conductivity chlorid discrepancy" in diabetes one type is usually permanent, the other always transient.

16 Van Slyke, Wu and McLean (Footnote 12) Donnan, F. G. The Theory of Membrane Equilibria, Chem. Rev. **1** 73 (April) 1924.

17 Foshay, Lee. The Relation of Hyperglycemia to the Relative Blood Volume, Chlorin Concentration and Chlorin Distribution in Dog's Blood, J. Exper. Med. **42** 89 (July) 1925.

In young, untreated diabetic patients there is evidence of some diminution of the blood alkalinity at all times. This rapidly disappears under insulin treatment.

In untreated, arteriosclerotic diabetic patients there is no evidence of diminished blood alkalinity unless the patient is nearly in coma.

In the case of extreme exsiccation from water deprivation given here, the blood picture is shown to be similar to that which occurs in acute diabetic coma. The chief differences are the greater retention of inorganic salts and a lesser glycemia.

THE PECULIAR FORMS OF INFECTION CAUSED BY THE BACILLUS OF TYPHOID FEVER

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Typhoid fever is perhaps one of the best studied diseases as regards pathogenesis, the clinical course and the anatomic changes that it causes. Thanks to the bacteriologic and biologic methods of investigation, however, we have found that it can take ever so many clinical forms and that it may simulate many morbid conditions. We also must state that it is necessary to make a strict distinction between typhus abdominalis proper and other infections caused by the bacillus of Eberth.

Typhoid fever is a general infection of the blood, Schotmuller's bacteriemia. Its localization in the lymphatic system of the alimentary tract is secondary and constant but not the only one possible. There are cases of typhoid starting with symptoms indicating the inflammation of the meninges, the kidneys or the lungs in which the presence of the Eberth bacillus in the blood is bacteriologically confirmed, the typical symptoms of typhus abdominalis, roseola, the characteristic behavior of the pulse and the temperature, the intestinal symptoms, etc., appear only in its further clinical course. French authors call this condition meningo-typhus, nephrotyphus and pneumotyphus. On the other hand, we see cases in which we fail to note any lesions of the lymphatic system or of the mucous membrane of the intestines with a positive result of the hemoculture and a positive Widal reaction, indicating the presence of the Eberth infection. Consequently, we must separate the typical typhoid fever from other infections that give a positive Widal reaction and an Eberth bacteriemia without the characteristic clinical symptoms and anatomic changes of typhoid.

Recently, we had an opportunity to observe in our wards a few cases of typhoid infection in various localizations entirely devoid of the clinical picture of typhus abdominalis, and probably without its characteristic anatomic changes.

REPORT OF CASES

CASE 1—A woman aged 33, unmarried, who had never borne children, complained of a cough with expectoration for the last fourteen days, a temperature reaching 38-39 C, stomach trouble with vomiting, and constipation. She thought that her trouble had begun after eating some cold meat. Twelve years before she had had typhus abdominalis. Five years before, an influenza with pneumonia, one year before, she had undergone an operation for the removal of the appendix.

On physical examination a distinct yellowish tinge of the eyes and the skin was found. There was a dulness with harsh breath sounds over the right apex, profuse dry crepitations in both lungs, and humid râles of a very fine character from the angle of the left scapula and from the horizontal nipple line downward. There were no changes in the heart. The pulse was 84, fairly full and regular. The liver was palpable 1 cm below the rib arch, soft and slightly painful on pressure, pressure of the right lumbar region caused pain.

In the urine, specific gravity was 1.026, there was 0.06 per cent of albumin, and there were traces of urobilinogen. Bile acids and bile pigments were absent, the diazoreaction was negative. In the sediment there were from 30 to 40 white cells and from 1 to 3 red cells on the field, endothelial cells from the upper urinary tract, and from 1 to 2 granular casts.

The stools were formed and brown, on examination under the microscope no red or white cells were present, the guaiac and benzidin tests were negative, hydrobilirubin was present.

The blood count revealed red cells, 3,920,000 per cubic millimeter, white cells, 7,600, platelets, 226,000 per cubic millimeter, hemoglobin, 74 per cent. The differential count was polymorphonuclear neutrophils, 74 per cent, lymphocytes, 23 per cent, transitionals, 2 per cent, and Turck's forms, 1 per cent. The direct van den Bergh test in the serum was positive after twenty minutes, the indirect gave 2.5 units of bilirubin. The Widal reaction in the serum was positive with the typhoid and the paratyphoid C bacillus in a dilution of 1:400.

During the first week after the patient's admission to the hospital, the temperature oscillated between 37 and 38 C, afterward it was normal with only slight oscillations from time to time.

The symptoms in the respiratory tract and the jaundice passed speedily during the third week. The pyelitis, however, was obstinate and yielded only after two intramuscular injections of milk, which caused a well defined reaction, namely, a rising of the temperature to 39.2 after the first injection and to 39.8 after the second. After seven weeks the patient was discharged almost completely recovered, a few white cells and an occasional endothelial cell in the sediment of the urine being the only traces of the pyelitis.

This case is interesting on account of the peculiar course of the infection, the nature of which there was no doubt as the Widal test was positive. In the absence of all clinical symptoms of typhoid fever, there was only the multilocular and characteristic localization of the infection, which attacked at the same time the liver (the parenchymatous jaundice), the respiratory tract (bronchitis sinistra inferior) and the kidney (pyelitis dextra). As these organs are the site of election for the Eberth bacillus, we felt that we had a typhoid fever infection and were inclined to make the Widal test.

Of course in this case we do not speak of typhus abdominalis, the lymphatic system of the alimentary tract was not clinically, nor to all appearances anatomically, affected. It was a typical infection, having its seat in many organs and caused by the bacillus of typhoid fever, perhaps in conjunction with *Bacillus paratyphosus* C. It also was impossible to decide, on account of the altered conditions of resistance, whether the morbid process arose in a typhoid carrier (the patient had had typhoid fever twelve years before) or if we had to do with a quite new infection independent of the infection twelve years before.

CASE 2—A woman, aged 48, with a rather unexpected localization of typhoid fever infection, complained of frequent stools, from twenty to thirty in twenty-four hours, with very distinct traces of blood, tenesmus, and pain in the lower part of the abdomen and in the left side. She said that she had been feverish. She attributed her trouble to a fall downstairs three days before. She had fainted on falling, and afterward felt a passing pain in the left side and in the lower part of the abdomen. She had never been ill before, had borne eight children, and had had no abortions.

On physical examination no changes were noticed, except a slight roughness of the breath sounds over the right apex and a slight pulsation in the jugular vein. The lower part of the abdomen was distended, and the right iliac region was a little painful. The spleen was palpable, the succussion of the left kidney, painful. A catheter specimen of the urine showed a trace of albumin, and on inspection under the microscope from 4 to 8 white cells in each field. A slight trace of blood and mucus appeared macroscopically in the stools. The Widal reaction was positive in a dilution of 1:400. On the eighth and ninth day of her stay in the hospital, the temperature, which until then had been about 37.6 C., rose to 38 and afterward fell to normal. The intestinal symptoms passed entirely by the end of the first week, and after two more weeks the patient was discharged, recovered.

We had here also, no doubt, an infection produced by the Eberth bacillus, under the form of an acute hemorrhagic inflammation of the large bowel, and an inflammation of the kidney pelvis (enteritis and pyelitis typhosa), all without any clinical symptoms of typhus abdominalis.

To another group belong the cases of the Eberth bacillus infection that begin with a picture of a grave gallbladder and bile duct infection, a severe jaundice, high temperature and peritoneal symptoms, and in the further course are complicated by bronchopneumonia, the high temperature curve and bed sores. This group of cases often resembles the grave forms of typhus abdominalis, the more as we find in them either the typhoid bacillus in the blood (bacteremia typhosa) or a positive Widal reaction in high dilution.

That we ought not to consider all these cases as typhoid fever but only as an infection with its primary seat in the liver and the gallbladder was proved by the following case.

CASE 3—A woman, aged 27, was admitted, March 31, 1924, complaining of attacks of pain in the region of the liver, recurring in the last five days several times in twenty-four hours, with jaundice and constipation. In 1914, she suffered from similar pain, without jaundice or temperature. In 1915, she had typhoid fever. In 1920, she had a return of the pain for eight weeks, and for the last year she had similar pains but with vomiting. She was married and had had four deliveries—three of the children died, one immediately after, one a few days after, and one a few weeks after birth. There was one living child.

Physical examination revealed a distinct yellowish tinge of the skin and the sclerae, a rather dry and furred tongue, a weakness of the fremitus and breathing over the lower part of the right lung, twenty-six respirations in one minute, the heart sounds rather loud and clear, pulse, 120, a tension of the skin and painfulness on pressure in the right half of the abdomen, the right liver lobe reaching the horizontal navel line, very painful on pressure, the spleen not painful and palpable on percussion from the ninth rib.

Analysis of the urine revealed albumin 15 per thousand, bile pigments, urobilinogen and urobilin, present, bile acids, absent, diazoreaction, negative, in the sediment of the urine from 20 to 30 white cells in each field and from 5 to 6 granular casts

The blood count was hemoglobin, 80 per cent, red cells, 4,000,000, white cells, 19,500, and platelets, 250,000 per cubic millimeter. The differential count was polymorphonuclear neutrophils, 90 per cent, lymphocytes, small and middle, 4 per cent, large, 5 per cent, transitionals, 1 per cent. Polymorphonuclear eosinophils were not found. Bleeding time was three minutes, coagulation time, seventeen minutes. Cholesterol in the serum was 198 per thousand. The direct test of van den Bergh in the serum was immediate and decidedly positive, the indirect, 8 units of bilirubin. The test for resistance of the red cells showed hemolysis in 0.26 per cent of sodium chloride while the control showed hemolysis in 0.36 per cent. A pure culture of Eberth bacilli, identified at the state epidemiologic institute, was received from the blood, the Widal reaction in the serum with the typhoid and the paratyphoid C bacillus was positive only in a dilution of 1:50. The stools were discolored, the sublimate test was negative, the blood test was negative.

During the next few days very distinct peritoneal symptoms appeared in the region of the upper right quadrant of the abdomen, simultaneously with a dulness and an evident weakness of the breathing sounds over the lower part of the right lung, posteriorly, and over the middle lobe in the front.

As the results of several exploratory punctures of the pleura at this point were negative and the symptoms were increasing, we thought of a subphrenical

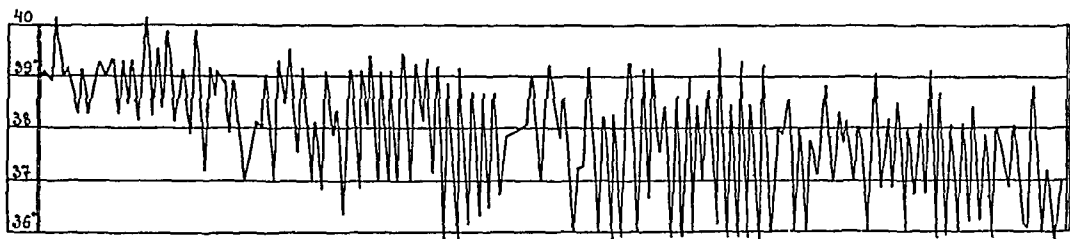


Fig 1—Temperature curve in Case 3

abscess, it was considered necessary to have recourse eventually to surgical intervention. However, in consideration of the grave condition of the patient and her decided refusal of such a proceeding, the operation was put off for a time.

The temperature, always at a high level, showed decided daily oscillations, with a tendency from time to time to fall gradually, but shortly returning to the same level. It was more than 39 in the evening, and 37 and 36.8 in the morning. The pulse, however, slackened from 120 to 100 a minute. The jaundice began slowly to disappear, the peritoneal symptoms passed, all the subjective complaints ceased, and the general condition of the patient, which until then had been almost hopeless, seemed to change for the better. On the other hand, diarrhea appeared, the spleen, which at the beginning was not palpable, became considerably enlarged, its lower edge reaching the horizontal navel line. The number of white cells in the blood decreased to 6,400 per cubic millimeter, whereas there were 19,000 in the beginning. The differential count revealed 75 per cent of neutrophils, there were 90 per cent before.

In the sacral region, in the region of both the greater trochanters, and in other places (for instance, on both sides of the chest) large and deep bedsores, which were now the real and principal cause of ailment, began to form. The general cachexia of the patient then reached a high grade. The result of hemoculture, two weeks after the first, was negative. The Widal reaction, however, positive before in the dilution of 1:50, rose to 1:400. (We must note especially that in many cases of cholelithiasis, with or devoid of jaundice, and with typhus abdominalis many years before, the Widal reaction in the serum always was negative.)

This condition lasted about three months. The morning and the evening temperatures always showed great differences but gradually commenced to fall. The bedsores, which were deep and putrid, began to heal nicely, the jaundice had long disappeared, leaving no traces. The pulse was fairly strong, in general not surpassing 100 beats a minute, but the cachexia was great and the patient died.

The macroscopic postmortem examination revealed that there were no affections of the mucous membrane of the intestine. The capsula of the liver, however, showed a considerable thickening and adhesions to the surrounding organs, the colon transversalis, the stomach and the diaphragm. The pylorus region was adherent to the lower surface of the liver. The gallbladder was small, shrunk and closely packed with stones. The hepatic, cystic and chole-dochus ducts were of a little fingerbreadth and filled with a quantity of stones, each the size of a medium sized bean and of irregular form. The liver, on being laid open, was completely covered with grayish green spots, from the size of a pinhead to that of a pea. In the center of each spot was the small aperture of a gall duct, besides many small cavities filled with pus, ranging in size from that of a small pea to that of a bean. In the right lobe, there was hardly any healthy tissue, in the left, the changes were not so extensive but were considerable. The diagnosis was cholangitis, pericholangitis purulenta and multiple hepatic abscess. The affections of the kidneys and of the heart corresponded to a chronic septic process.

Two factors contributed toward the peculiar infection in this case (1) the previous typhoid, after which the microbes remained somewhere in the organism, probably in the gall canals, in order that at a proper moment, overcoming all resistance, they might get into the blood and attack the organism, (2) an old gallbladder disease, which formed in the liver—the place most disposed to catch infection—a *locus minoris resistentiae*.

In our fourth case we had generally a similar course of events but in lighter form.

CASE 4—A woman, aged 43, complained of a jaundice and sharp pain in the region of the liver, radiating toward the right shoulder-blade and the lower ribs, the pain being of three days' duration. The patient had this pain with vomiting for the first time three months before, the vomiting was followed by jaundice. She was under a physician's care for five weeks, after which she felt quite well until her present illness. She had never been ill before, she had five normal deliveries and afterward four pregnancies that terminated before the third month.

The physical examination showed a distinct yellowish tinge of the skin and the sclerae, a slight dulness over the right collar-bone and in the back, a weakness of the breath sounds over the lower part of the right lung, the second sounds at the base of the heart fairly strong, the second aortic sound, accentuated, the abdomen distended, especially in its lower part, a distinct muscular resistance (*defense musculaire*) in the right half of the abdomen, most considerable in the upper quadrant, pain in the abdomen on pressure which was slighter on the removal of pressure, the spleen not palpable, palpation of the liver impossible on account of the distended state of the abdomen, the tendinous reflexes present, temperature, 39 C, pulse, 128, and respiration, 28.

Examination of the urine revealed specific gravity, 1.024, albumin, 0.4 per thousand, a trace of urobilinogen, a doubtful trace of the bile pigments. Hay's test was positive, the diazoreaction was negative. In the sediment there were a few cells and from one to two granular casts in the microscope field. Hemoglobin totaled 98 per cent, red cells, 4,300,000, white cells, 14,800. The differential count was polymorphonuclear neutrophils, 72 per cent, lymphocytes, 26 per cent, platelets 150,000. The bleeding time was two minutes, the coagulation time, six

minutes. By the van den Bergh test the bilirubin in the serum was about 3 units, the direct test was positive after one minute. The Wassermann reaction in the serum was negative, the result of the hemoculture was negative. In the feces the Schmidt test was positive, blood was not found, and on inspection under the microscope no white cells were discovered.

During the next four or five days, the temperature became subfebrile, the abdominal symptoms passed almost completely, the liver was now palpable three fingerbreadths under the edge of the rib, hard, smooth and sore, the jaundice passed, the albumin, bile acids and granular casts disappeared, leaving no trace. The diazoreaction remained negative. On the other hand, a dullness with an almost complete absence of breath sounds appeared over the lower part of the right lung and over the region of the right angle of the shoulder, egophony and bruit de souffle.

The condition of the patient, after a passing improvement, became considerably worse, the temperature rose and disturbing pain appeared in the right side. Exploratory punctures of the right pleura, repeated twice, each gave 3 cc of a turbid liquid, with a considerable amount of fibrin and 5 per cent of albumin. The differential count of the liquid sediment was as follows: 75 per cent neutrophils, 23 per cent lymphocytes and 14 per cent endothelial cells.

During the patient's first week in the hospital, diarrhea changed to constipation. The process continued in this way for about two weeks, during which numerous râles of a fine character appeared on the right axillary line, with tubular breath sounds in the region of the fourth and fifth ribs (on the same line). A dullness, beginning from the angle of the shoulder-blade posteriorly and from the upper edge of the fourth rib in the front, still continued. The temperature was intermittent. The patient felt generally bad. Under the arch of the ribs, the edge of the spleen became palpable. The sacrum and the feet became swollen. A second exploratory puncture of the pleura gave a negative result. A renewed blood examination showed 9,600 white cells, neutrophils, 74 per cent, lymphocytes, 23 per cent, monocytes and transitionals, 3 per cent. Bilirubin in the serum totaled 0.8 units. Nothing particular was noted in the urine. The continued fever, the simultaneous occupation of the liver and the lungs by the affecting factor and the swelling of the spleen suggested the typhoid infection and the Widal reaction in the serum, which was positive in a dilution of 1:400 with typhoid bacilli (negative with paratyphoid A and B bacilli), confirmed our supposition that we had to do with a typhoid infection. The further course of this case did not give any particular result. During the fourth week, the temperature began to be nearly normal, the pulse from 100 and 96 slackened down to 84, the pulmonary symptoms passed little by little, and the patient after a two month stay in the hospital, was discharged as healthy.

A year and a half before this article was written, we observed a fifth case, quite analogous to the foregoing two, which we shall mention only, and which as regards graveness, ranked between these two cases.

CASE 5—A woman complained of symptoms of cholecystitis and cholangitis purulenta, with a distinct jaundice, high temperature and considerable leukocytosis with neutrophilia. Typhoid fever existed in the history of the illness. In the further course an inflammation of both lungs appeared, with extreme cachexia and bedsores. After only four or five weeks, when the temperature began to fall and the patient to recover, the characteristic appearance of the temperature curve on the chart, suggested typhoid infection. (It was our first case of that type.) The Widal reaction in the serum was decidedly positive even in the dilution of 1:800, and the hemoculture was negative.

The further favorable course of the illness, in spite of the critical condition of the patient, the speedy healing of the bedsores, the amazingly quick return of strength, and the general recovery left no doubt as to the typhoid nature of this case.

In all these cases, except Case 2, the typhoid infection took the form of an acute illness of the liver and bile ducts, with jaundice, leukocytosis and neutrophilia, although in its further course, we observed symptoms of typhus abdominalis, diarrhea, swelling of the spleen, etc. On post-mortem examination in Case 3, none of the characteristic changes of typhoid fever were seen, especially no affections of the mucous membrane of the intestine. Also jaundice during typhus abdominalis is a rarity. In the 300 such cases that passed through our hands in the time of the epidemic of 1922, jaundice appeared in only one case, during a fairly grave relapse of the sickness. Jurgens,¹ for instance, when discussing several variations and peculiarities in the course of typhoid, accentuates the fact that "jaundice is a great rarity, even a very slight yellowish tinge being such an unusual phenomenon that the presence of this symptom speaks against the diagnosis of typhus abdominalis." As a fact of particular interest, we may mention that in our cases, in spite of the process being caused by the typhoid bacillus, and this bacillus being received in a pure culture from the blood (Case 3), we met with a high leukocytosis with neutrophilia, as in every acute infectious process. It is therefore obvious that the characteristic feature of typhoid fever, leukopenia with neutropenia, does not depend on some special qualities of the Eberth bacillus itself nor on its presence in the blood, but is due to its localization in the lymphatic system.

In case of a different localization of this bacillus, the organism reacts on the typhoid infection not with leukopenia but with leukocytosis.

The observation of Naegeli agrees with our supposition. He says that during the first two days of typhus abdominalis the number of white cells in the blood increases at the cost of neutrophils and that the neutropenia appears only afterward. Probably at the beginning of typhus abdominalis we have to do exclusively with a general infection without a special localization in the lymphatic system of the alimentary tract. During this period of typhus abdominalis just as in our cases, the organism reacts, on the invasion of the Eberth bacilli, with leukocytosis and neutrophilia.

To our knowledge there are in the medical literature few cases similar to the one mentioned in the foregoing. In 1901 Besançon² published a case of the cholecystitis catarrhalis with the temperature resembling typhoid but without the period of continuation and without the clinical symptoms of typhus abdominalis, the Widal reaction being positive in a dilution of 1:600.

1 Jurgens, S. Spezielle Pathologie und Therapie inner Krankheiten. Kraus und Bruggsch 2.

2 Besançon, M. F. Semaine med., 1901, p. 396.

Based on these grounds, the author states that the Eberth bacillus can behave like a simple saprophytic microbe and evoke quite a common illness, analogous with our first case

Leignel-Lavartine ³ describe an acute inflammation of the gallbladder and of the surrounding tissues during typhus abdominalis

Abram and Gautier ⁴ noticed a case of obstructive jaundice with complete retention of the bile pigments, but without the retention of the bile acids (a completely dissociated jaundice) in the course of typhus abdominalis. Postmortem examination revealed the exclusive disease of the parenchymatous tissue of the liver, hepatitis diffusa, without the slightest affection of the larger and the smaller gall ducts

Guion and Gendron ⁵ give an interesting case bearing great resemblance to our Case 3, the patient, being a child, aged 5 years. A few days after its father's death from typhus abdominalis, temperature appeared, after ten days, the obstructive jaundice with splenomegalia, on the twenty-seventh day, the jaundice subsided and the classic picture of typhoid fever developed, with roseola, involvement of the lungs, etc

In 1911 Janowsky ⁶ also published a case of a grave typhus abdominalis, in which after three weeks general indisposition with temperature the jaundice appeared together with vomiting. The author, who at this period was called to the patient for the first time, found a considerable enlargement of the liver and the spleen, the abdomen distended and painfulness in the right iliac region. He diagnosed typhus abdominalis. The diagnosis was afterward confirmed by the positive result of the Widal reaction in the serum, 1:120, and by an almost imperceptible intestinal bleeding in the further course. This case, considered by the author as a rare form of typhus abdominalis, is similar to the mentioned case of Guignon and Gendron, it differs, however, from our last three cases in that the jaundice appeared after a three weeks illness, while in our cases the affection of the liver appeared at the beginning, a fact that makes our cases still more interesting

The peculiarity of our cases that should be especially accentuated is that the typhoid infection passed without the implication of the intestinal lymphatic system

As corresponding to the foregoing cases, especially Case 3, we mention the last case under our observation, a liver abscess, caused, it is true, not by the typhoid but by the paratyphoid A bacillus, on the

3 Leignel-Lavartine. Séance de la Soc. Méd. d. Hopitaux, Feb. 14 and Feb. 21, 1909, Semaine méd., 1909, p. 249

4 Abram and Gautier. Séance de la Soc. Méd. d. Hopitaux, Dec. 13, 1912, Semaine méd., 1912, p. 610

5 Guion and Gendron. Séance de la Soc. Méd. d. Hopitaux, Dec. 16, 1910, Semaine méd., 1910, p. 607

6 Janowsky, W. Gaz. lek., 1911, p. 19

grounds of an old and chronic inflammation of the gallbladder and the surrounding tissues

CASE 6—A woman, aged 60 complained of pain in the region of the right rib arch, with shivering, vomiting and, according to her statement, feverishness. When she was questioned further, it appeared that for the last ten years she had suffered from similar attacks of pain, which occurred seldom in the beginning, once or twice in a year, but lately every two or three months, especially in the night, they lasted a few hours and were never accompanied by jaundice. At the age of 14, she was supposed to have had typhoid fever. On physical examination, nothing particular was found, except a slight accentuation of the second pulmonary sound and a slight painfulness under the right rib arch. In the catheter specimen of the urine, except an occasional white cell in the microscopic field, nothing particular was noted. The temperature during the first four days of her stay in the hospital was normal. On the fifth day it began to rise in a fairly irregular way to 40° C., and after staying at this level from twenty-four to forty-eight hours fell to 38 and 36°

In the meantime, the condition of the patient became as bad as was possible. A state of complete numbness speedily ensued. There were however, no subjec-

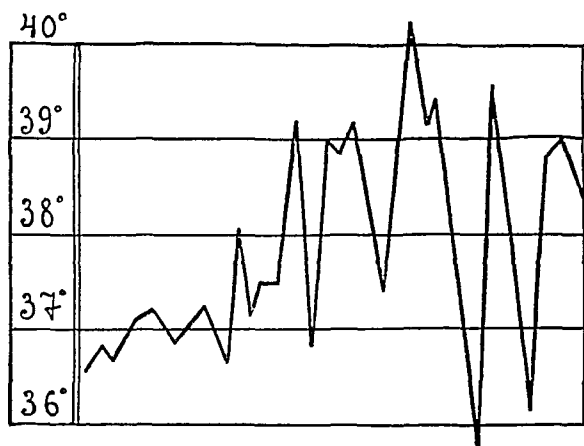


Fig. 2—Temperature curve in Case 6

tive complaints and no possibility of determining any affections, except a slight sensitiveness under the right rib arch and a slightly marked Murphy's sign. Nevertheless, the bad pulse (always more than 100), the constant numbness, the raspberry colored, dry tongue, the dry throat and the diarrhea (from three to four liquid stools in twenty-four hours), all gave the picture of a grave illness, with the diagnosis oscillating between typhus abdominalis and tuberculosis miliaris acuta.

At the beginning of the fever state, the blood count revealed 5,400 white cells per cubic millimeter. The differential count was neutrophils, 58 per cent, lymphocytes, 38 per cent, and transitionals, 4 per cent. After seven days the repeated examination revealed 11,800 white cells per cubic millimeter, the differential count being neutrophils, 85 per cent, and lymphocytes 12 per cent. The bilirubin in the serum was 0.7 units, van den Bergh, cholesterol, 0.28 per thousand. The Wasserman reaction was negative. The hemoculture on sugar, bouillon and bile was negative.

The Widal test in the serum, performed on the fifth day after the patient's temperature first rose on the ninth day of her stay in the hospital, was negative with the typhoid and the paratyphoid B bacillus, and positive with the paratyphoid A bacillus in the dilution of 1:400. Five days later, the repeated test was again positive only with paratyphoid bacillus in a dilution of 1:100.

The examination of the urine showed albuminuria 0.2 per thousand, red cells, and endothelial cells from the upper urinary tract. The diazoreaction remained negative. Gall acids and gall pigments were absent. No remarkable abdominal symptoms were present.

On the sixteenth day of her stay in the hospital and twelve days after her temperature first rose, the patient died.

The postmortem examination revealed the following conditions. The gallbladder was small, shrunken and quite hidden in adhesions, with the surrounding tissues and the lower liver surface. No stones were present. An abscess was found boring into the depth of the right liver lobe and reaching the region of the gallbladder neck. There were glomerulonephritis, enlargement of the spleen, and septic tumor, a degeneration of the parenchymatous organs, the liver and the heart muscle. This case is unusually interesting: (1) as an example of the possibility that the gallbladder may be inflamed for many years without the formation of stones, (2) as an evident liver abscess that arose on the grounds of the infection with paratyphoid A bacillus, whose presence was not disclosed by any remarkable clinical symptom.

It is difficult to judge in Case 6 if we had to do with a sudden augmentation of the virulence of the paratyphoid A bacilli in the organism, which for a long time had been their carrier and in which they caused a chronic inflammation of the gallbladder, or if it was a fresh invasion of the gallbladder by the paratyphoid A bacilli, the gallbladder being free from typhoid infection though affected by a former illness.

The only way to clear up this doubt would be to make the Widal test in the serum during the period preceding the pyretic state. The positive result of this test would indicate that we had to do with a constant carrier of the micro-organisms, the negative, in addition to the later results, would favor a fresh and independent infection.

CONCLUSIONS

1 The existence of typhoid bacteriemia and a positive Widal reaction in high dilution, 1:400, 1:800, along with a high temperature is not always an absolute proof of typhus abdominalis.

2 The mentioned conditions may be observed in states of typhoid infection, located most often in the liver and the gallbladder.

3 Such states of typhoid infection, although in some sense similar to typhoid fever, differ from the latter in (a) the presence of leukocytosis with neutrophilia, (b) the absence of roseola, and (c) the absence of the changes in the lymphatic system of the alimentary tract.

4 The leukopenia with neutropenia, one of the most characteristic symptoms of typhus abdominalis, probably does not depend on the biologic quality of the typhoid bacillus but on its secondary seat in the lymphatic system of the alimentary tract.

THE EFFECT OF HEART MUSCLE DISEASE ON THE ELECTROCARDIOGRAM *

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Pathologists and clinicians have long been engaged in the correlation of the symptoms and signs of heart failure with the condition of the heart as found at necropsy. With the advent of the electrocardiograph, investigators promptly began to make comparisons between the normal and abnormal function of the heart and the electrical current produced by that organ. This correlation has led to a quite thorough understanding of the mechanism of cardiac arrhythmia.

The correlation of structural disease of the heart with abnormalities of the electrocardiogram has proceeded more slowly, and it has been our purpose to report in detail a series of cases in which the gross and microscopic appearance of the ventricular muscle is compared with the ventricular complexes of the electrocardiogram. We are endeavoring to decide whether an abnormal ventricular complex must mean myocardial disease and whether a normal ventricular complex will be produced by only a normal muscle. We are able from this study to throw some light on the relation between certain abnormalities of the ventricular waves of the electrocardiogram and the type of pathologic change within the heart muscle.

Previous work has been especially concerned with the association of particular abnormalities of the waves with particular pathologic changes. It is our aim to attack the more general problem of the relation between the electrocardiogram and heart muscle disease.

The electrocardiogram of the normal heart beat consists of the P wave, due to auricular activity, and the Q-R-S group and the T wave, which are the result of ventricular action. There are certain features of these waves which have been found to occur in records from normal hearts and others which have been found only in records from hearts suspected of being abnormal.¹

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¹ Pardee, H E B, and Master, A M. Electrocardiograms and Heart Muscle Disease, J A M A 80 99 (Jan 13) 1923. Pardee, H E B. The Clinical Aspects of the Electrocardiogram, New York, Paul B Hoeber, 1924.

Einthoven's signs of hypertrophy of the right or left ventricle² are now considered to indicate the direction of the predominant electrical effect of the Q-R-S group rather than solely a muscular hypertrophy³. These changes do not indicate pathologic muscle, though they may indicate one that is hypertrophied.

Notching of the Q-R-S group is an abnormal feature if found near the peak of a wave in the lead giving that wave a relatively large excursion. It will, under these circumstances, be associated with a notching or slurring of the Q-R-S group in one or both of the other leads. Prolonged duration of the Q-R-S group is abnormal if the prolongation exceeds 0.1 second, but in a heart that is much enlarged or that gives a record of marked left predominance 0.12 second may be considered normal.

A voltage of the Q-R-S group so low that its size does not exceed 5 mm in the lead of largest excursion is a significant abnormal finding. If the T wave is turned downward in Lead I or Lead II, or both, it is an abnormal feature. Moreover, there is a special form to the T wave which is believed to be characteristic of coronary artery occlusion with an area of deficient blood supply in the ventricular muscle. The wave shows an upward convexity followed by a sharp downward peak in one lead. If this occurs in Lead III alone it is not significant unless T₂ is turned downward, although T₂ need not show the peculiar upward convexity.

Certain combinations of these abnormalities tend to occur together frequently. Perhaps the most common combination is the "arborization block" of Oppenheimer and Rothschild⁴ in which a prolongation of the Q-R-S complex beyond 0.1 second, notching of the R wave and low voltage occur.

Another common form of abnormal curve is considered to indicate bundle branch block. In this case a notched Q-R-S group occurs with a lengthening of the duration to 0.14 second or more. The chief deflection here is either upward in Lead I and downward in Lead III or vice versa. The Q-R-S group turns smoothly into the T wave, which is directed opposite to the chief deflection of the Q-R-S group.

Our studies are concerned with eleven hearts obtained at the New York Hospital from patients who died of heart failure. They were from the medical services of Drs. L. A. Conner and W. R. Williams. The hearts were turned over to us for microscopic examination and we

2 Einthoven, W. Weiteres über Elektrokardiogram, *Arch f d ges Physiol* **122** 517, 1908.

3 Lewis, T. Observations on Ventricular Hypertrophy, with Especial Reference to Preponderance of One or Another Chamber, *Heart* **5** 367, 1913-1914.

4 Oppenheimer, B. S., and Rothschild, M. A. Electrocardiographic Changes Associated with Myocardial Involvement, *J. A. M. A.* **69** 429 (Aug 11) 1917.

noted the gross and detailed findings. Sections were taken from the lateral wall of each ventricle, from the interventricular septum in its middle portion and from the right auricular muscle. These were stained with the ordinary hemotoxylin eosin and with Herxheimer's scharlach r as described by Mallory and Wright ⁵

As controls, similar sections from thirteen normal hearts were obtained at the Bellevue Morgue (New York City) through the courtesy of Dr. Douglas Symmers. These hearts were from persons who averaged about 30 years of age and had met a sudden death, e. g., by bullet, stab wound or fall, and whose viscera were apparently free from disease. The same stains were used in this series as in the pathologic hearts.

It was only after thorough study of slides from similar portions of the hearts of the control series that we felt able to decide what should be called normal heart muscle. We found particularly that the picture which most pathologists would call fatty degeneration was often present in the normal hearts of our control series ⁶. In other words, we found that cardiac muscle normally contains a considerable amount of microscopically demonstrable fat, so we were not so ready to report fatty degeneration of the fibers as we might otherwise have been.

We also were able to gauge more accurately how much connective tissue should be found between the muscle cells and the bundles and how much round cell infiltration could be considered normal.

We feel quite certain that many authors have reported fatty degeneration of the heart when this condition was not present. Had it not been for the controls we should certainly have wrongly considered that some of our pathologic hearts showed fatty degeneration or diffuse round cell infiltration or both.

In our present series we have considered the slightest departure from normal to be an increase of the cells of the interstitial fibrous tissue (Fig. 9). As this progresses it leads to what has been called fibrous tissue replacement, the microscope showing more or less dense bands of fibrous tissue between or within the muscle bundles (Fig. 14). When this is extreme it leads to a change in the macroscopic appearance of the muscle. This picture may possibly come about at times through a primary degeneration of muscle fibers with secondary fibrous replacement. We also noted patches of fibrous replacement with relatively little muscle tissue, which had resulted from old infarcted areas.

We do not feel persuaded that such apparent changes as thinning or thickening of the individual muscle fibers, fragmentation, cloudy degeneration or even fatty degeneration, as it is usually diagnosed from the

⁵ Mallory and Wright. *Histological Technique*, Ed 7, p. 167.

⁶ Master, A. M. Fatty Degeneration of the Heart, *Arch. Int. Med.* **31**: 221 (Feb.) 1923.

Case	Diagnosis	Electrocardiogram Ventricular Waves	Heart	Coronary Arteries	Microscopic Examination
1	Chronic interstitial nephritis, chronic arteriosclerosis	Borderline r v p, downward T wave in all leads (digitals)	Enlarged, 600 gm	Slight coronary atheroma	Muscle normal
2	Aortic stenosis and regurgitation, mitral stenosis, aortic fibrillation, tertiary syphilis	Borderline l v p downward T wave in all leads (digitals)	Enlarged, 540 gm	Markedly thickened and calcified, no narrowing or occlusion	Muscle normal except for slight fibrous replacement in left portion of interventricular septum
3	Rheumatic mitral stenosis and regurgitation, heart block	Slight l v p	Large, 425 gm	Moderate atheroma, no narrowing	Muscle practically normal possibly a slight increase in fibrous tissue
4	Rheumatic aortic regurgitation, mitral regurgitation and stenosis acute pericarditis with adhesions	Normal except Q-R-S = 0.12 sec and	Greatly enlarged, pericardium adherent in many places	Normal	Muscle normal except for slight invasion of the inflammatory process from pericardium
5	Coronary thrombosis, chronic arteriosclerosis	R v p, T wave downward in Leads II and III and in Lead III, with an upward convexity before the downward peak	Large 500 gm, large pale focus on posterior surface of left ventricle where fibrous replacement was the predominant feature in section	Thickened lumen of anterior descending branch occluded by thrombosis at its first main division	On posterior surface of left ventricle and in lower part of the septum, especially on the left side, areas of necrosis of the muscle with the usual accompanying inflammatory reaction, muscle of right ventricle normal except for slight increase of interstitial tissue
6	Chronic arteriosclerosis coronary artery disease, chronic myocarditis	Borderline l v p small Q-R-S excursions R = 6 mm downward T wave in Leads I and II	Much enlarged, 875 gm endocardium appeared normal wall of left ventricle thinned and had scattered gray areas	Diseases and had calcareous deposits, left artery especially involved and for 3 cm almost obliterated	Marked increase of interstitial fibrous tissue and some fibrous replacement, right ventricle had only increase of interstitial tissue
7	Chronic arteriosclerosis, chronic myocarditis	All waves very small downward T wave in Leads I and II	Much enlarged, surface fat abnormally widespread and thick and left ventricle muscle somewhat thinned	Markedly thickened and calcified and narrowed throughout, but no occlusion	Considerable fibrous tissue replacement in left ventricle and in septum no replacement, but moderate crease of interstitial fibrous tissue
8	Chronic arteriosclerosis chronic myocarditis with fibrillation	Marked l v p, Q-R-S group notched downward T wave in Lead I	Markedly enlarged, 640 gm, left ventricle had numerous small areas of fibrosis, and it apex a thinned, fibrous, partly calcified area patchy sclerosis of the endocardium especially at apical part of left side of septum	Marked atheroma with narrowing, especially in anterior descending branch of left coronary, which was almost obliterated	Muscle had marked increase of interstitial fibrous tissue no fibrous replacement except in area at apex of left ventricle right ventricle had only slight change
9	Chronic arteriosclerosis chronic interstitial nephritis gangrene of lung, broncho pneumonia	Marked l v p, Q-R-S group notched, downward T wave, Leads I and II	Much enlarged, 740 gm, endocardium of both ventricles thickened especially on septal surface of left ventricle	Extensive atheromatous plaques, little thickening no occlusion	Muscle showed diffuse but only slight increase of interstitial fibrous tissue, septal endocardium of left ventricle much thickened
10	Chronic arteriosclerosis chronic interstitial nephritis, aortitis, uricular fibrillation	Wide Q-R-S group, notched Q-R-S group, curve suggests partial lesion of right branch auriculoventricular bundle	Much enlarged, 575 gm, left ventricle thinned toward apex, endocardium of right ventricle thickened in region between anterior and posterior papillary muscles	Stiffened and tortuous, no occlusion	Muscle in left ventricle had numerous dense patches of fibrous tissue replacement elsewhere moderate to marked increase of the interstitial fibrous tissue
11	Rheumatic mitral stenosis mitral regurgitation	Small waves, wide Q-R-S group, notched Q-R-S group downward T wave in Leads II and III	Large, 475 gm, muscle and endocardium appeared normal except for diseased mitral valve	Little or not at all thickened, slight atheroma, no narrowing	Muscle had considerable fibrous tissue replacement, especially marked in the left ventricle but not accentuated in subendocardial muscle layers

presence of fat droplets within the muscle fibers, actually mean anything more than a varying technic of staining or fixing or cutting of the sections

The case histories, electrocardiographic and pathologic findings which follow are briefly summarized in the accompanying table

REPORT OF CASES

CASE 1—A man, aged 51, was admitted four times to New York Hospital. In 1911 he entered the institution for chronic lead poisoning and pyorrhea alveolaris and in 1913 he had an abscess of the lung. Dec 1, 1920, he was admitted for bronchial asthma, but features of chronic interstitial nephritis, arteriosclerosis

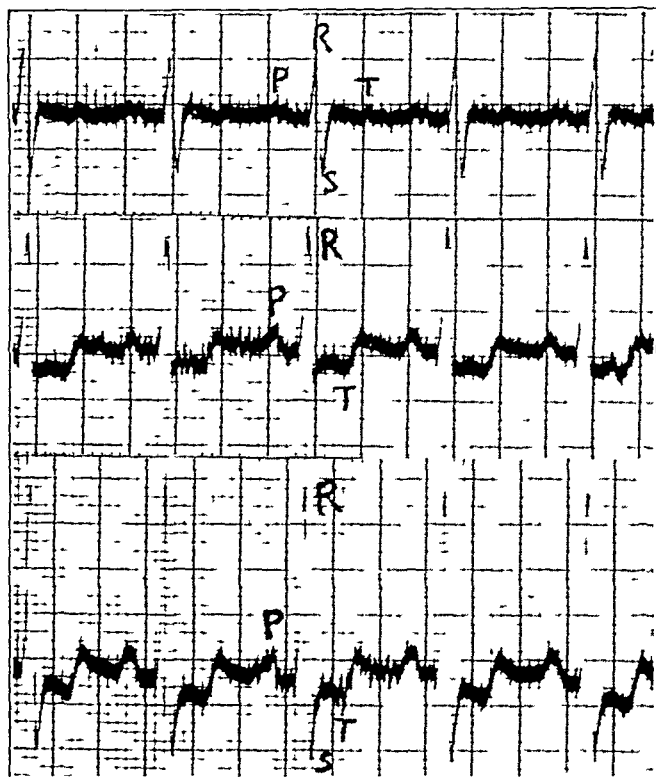


Fig 1 (Case 1)—Q-R-S group, showing right predominance, the T waves are downward in Leads I and II

and chronic lead poisoning were present. He was discharged Jan 9, 1921. The patient was admitted for the last time January 21, and died February 7. He was orthopneic and weak and suffered severely from attacks of paroxysmal dyspnea. His lungs contained many râles suggesting bronchial asthma. In December, 1920, his heart was enlarged 2 cm to the right and 13 cm to the left of the midsternal line in the fifth space, and a soft systolic murmur was heard at the apex. At the end of January, 1921, the dullness of the heart had increased to 16 cm to the left in the sixth space and 3 to the right in the third space. A gallop rhythm was present. Sounds at the apex were muffled. The radial vessels were sclerotic. The liver palpated 4 cm below the costal margin.

The blood pressure ranged between 190 and 210 systolic, and 90 and 110 diastolic. The urine had a specific gravity of 1.012-1.015, with albumin and granular and epithelial casts. The urea nitrogen was 64-71 mg and creatinin 4.2-4.6 mg.

The electrocardiogram three days previous to death (Fig 1) showed a Q-R-S group on the borderline of right ventricular predominance. The T wave was sharply downward in Leads II and III, and slightly so in Lead I, but the patient had received about 700 minims of the tincture of digitalis during the previous thirteen days.

The necropsy diagnosis was chronic interstitial nephritis, hypertrophy of the heart, edema of the lungs, chronic fibrinous pleurisy, arteriosclerosis of the aorta, and fibroma of the kidney.

Gross examination of the heart showed that it was much enlarged, weighing 600 gm, and that the walls of both ventricles were thickened. The valves and muscle appeared normal. The coronaries showed a few small, roughened areas in the intima. The aorta showed very slight arteriosclerosis with a few scattered noncalcified plaques.

Microscopic examination of the heart muscle revealed no abnormality and no fatty degeneration.

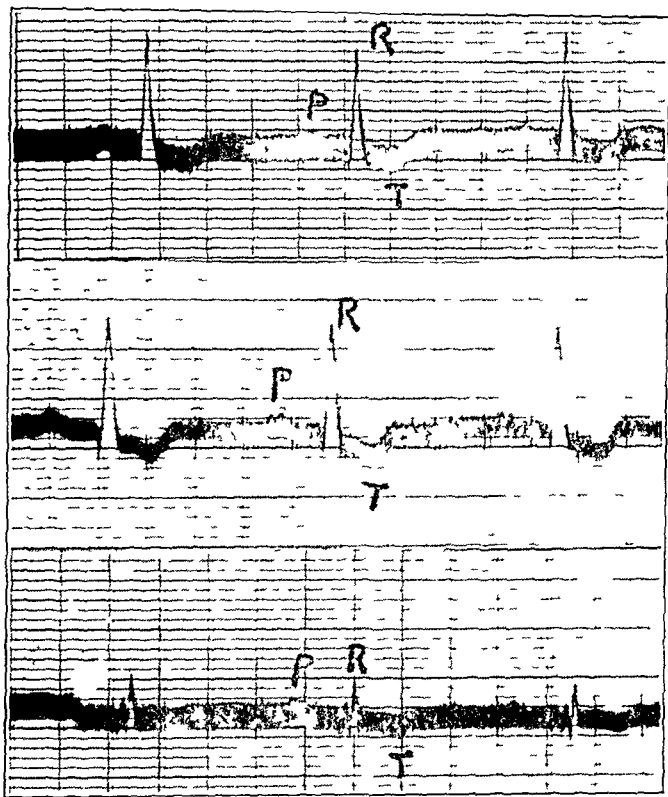


Fig 2 (Case 2) —Normal Q-R-S group, the downward T waves of Leads I and II probably are a digitalis effect.

CASE 2—A man, aged 65, who was admitted Nov 11, 1916, and died December 22, had complained of shortness of breath, especially on exertion, and of palpitation, cough, and swelling of ankles from May onward. He was dyspneic and orthopneic on examination, and diffuse, squeaky râles were present in the chest. The heart was not enlarged, but the action was completely irregular, suggesting auricular fibrillation. There was a loud systolic murmur at the apex and a blowing diastolic murmur over the base and body of the heart, as well as a rough systolic murmur and a systolic thrill at the aortic area. The liver was palpable. The blood pressure ranged between 150 and 180 systolic and was 50 diastolic. The urine showed a faint trace of albumin, with granular casts, the nonprotein nitrogen was 69 mg. Before death the patient complained of pain in the right leg.

The electrocardiogram five days before death (Fig 2) showed a prolonged auriculoventricular conduction time, 0.24 second. The Q-R-S group was on the

border of left ventricular predominance. The T wave was downward in all three leads, which may be explained by the patient's marked digitalization (November 10-12, 150 minims of the tincture, November 12-16, 240 minims, and November 16-December 11, 30 minims were given twice a day.)

At necropsy the diagnosis was chronic valvular disease, hypertrophy of the heart, chronic nephritis, general arteriosclerosis, hydrothorax, chronic pleurisy, and thrombosis of the right tibial artery.

The gross examination of the heart showed an organ considerably enlarged, weighing 540 gm. Both mitral and aortic valves were thickened and calcified, and the orifices, especially the aortic, were stenosed. The muscle appeared normal. The coronaries were markedly thickened and calcified. There was moderate narrowing but no occlusion. The aorta showed numerous areas of atheroma especially in the abdominal portion.

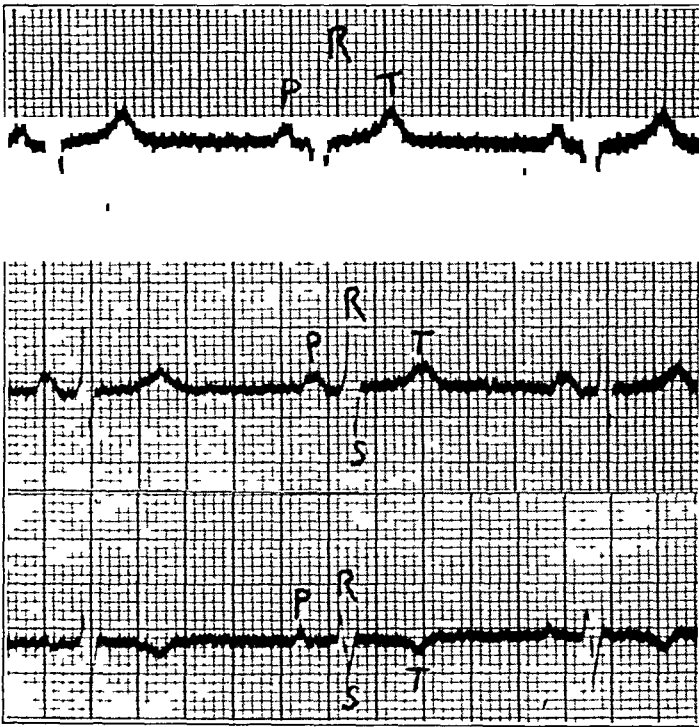


Fig. 3 (Case 3) —Normal record except for slight left predominance of the Q-R-S group

Microscopic examination revealed no abnormality of the ventricular muscle except for an area in the left portion of the interventricular septum where there was a slight degree of fibrous tissue replacement. No fatty degeneration was found.

CASE 3—A man, aged 52, gave a history of spells of weakness, palpitation and fainting from December, 1919, to April, 1920. These attacks were typical of Stokes-Adams' disease. There was an interval of freedom from attacks for one month. However, these recurred in June and the patient died July 3, 1920.

During life the heart was only slightly enlarged, and presented a complete heart block with the auricles beating at the rate of 100 and the ventricles at 27, except during the one month period of freedom, when the conduction time was normal. A soft blowing systolic murmur was heard at the apex. The blood pressure ranged between 140 and 180 systolic, and 70 and 100 diastolic. The urine showed a faint trace of albumin, the nonprotein nitrogen was 38 mg. The Wassermann reaction was negative.

The electrocardiogram taken 11 days previous to death (Fig 3) showed a ventricular complex with a slight left predominance but with no other abnormality

The necropsy diagnosis was chronic myocarditis, chronic cardiovalvular disease, chronic interstitial nephritis, right hydrothorax, cirrhosis of the liver, general arteriosclerosis, and edema of the lungs

The gross examination of the heart showed that it was moderately enlarged, weighing 425 gm. The mitral valve was thickened and contracted, the left auriculoventricular ring was calcified for about three fourths of its circumference. The left ventricle was hypertrophied, the muscle appeared to have some increase in fibrous tissue but had no focal lesions. The left auricular wall was thickened

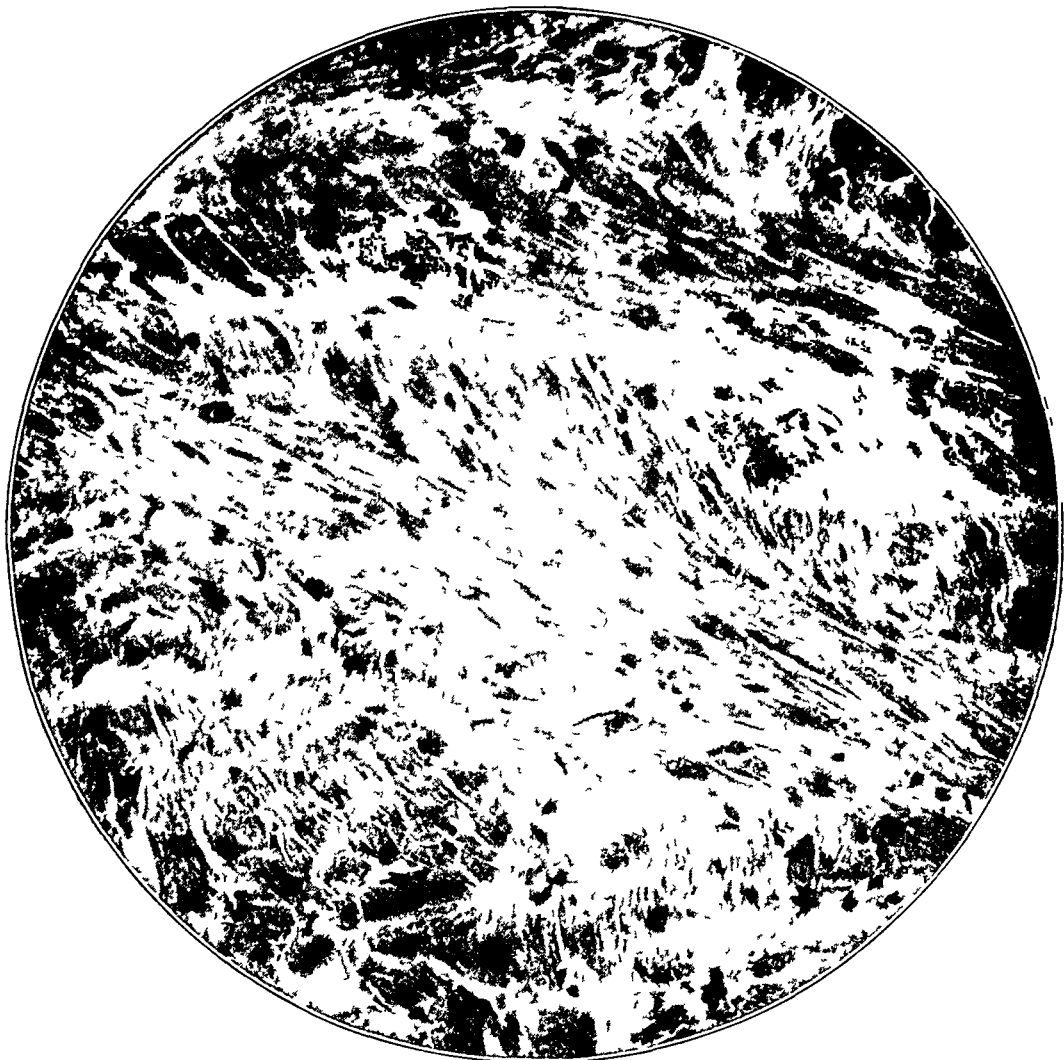


Fig 4 (Case 3)—Practically normal muscle, with little if any increase of interstitial connective tissue, at the top, a blood vessel cut longitudinally

as was the endocardium of this chamber. The coronaries showed moderate atheroma but no narrowing. The aorta was moderately atheromatous.

The microscopic examination revealed a practically normal muscle with very little if any increase of interstitial connective tissue (Fig 4). There was no fatty degeneration.

CASE 4—A man, aged 22, whose first admission dated from June 4 to July 19, 1920, was admitted for the second time July 26 and died Feb 7, 1921. At the first admission he complained of abdominal cramps, he was operated on but no diseased condition was found. After this operation, he complained of shortness of breath, palpitation, cough and finally swollen legs. The heart percussed

15 cm to the left of the midsternal line in the sixth space, 7 cm to the right in the fourth space. A systolic thrill and a diffuse impulse were present over the entire precordium. The patient showed the murmurs of aortic regurgitation and of mitral regurgitation and stenosis. The liver was palpated to the level of the umbilicus. The patient developed fluid in the pericardial sac. The blood pressure was 130 systolic, 75 diastolic. The specific gravity of the urine was from 1.022 to 1.033, there was a very faint trace of albumin, and granular casts were present at times.

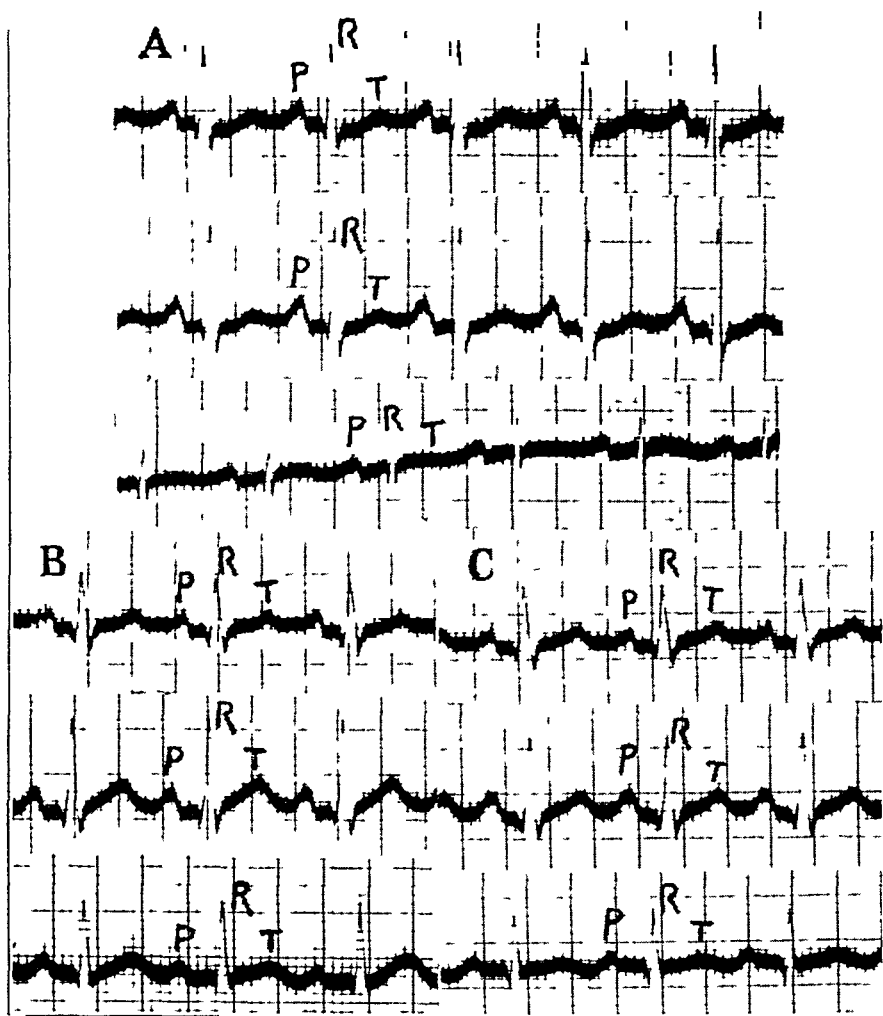


Fig 5 (Case 4) —*A*, record of January 25, showing a Q-R-S duration of 0.1 second. *B*, record of February 5 before the pericardial tapping, with a Q-R-S duration of 0.12 second. *C*, record of February 5 after the tapping.

The electrocardiogram, Figure 5 *B* and *C*, taken two days before death, showed no abnormality (but see text) except a Q-R-S duration of 0.12 second. There was no ventricular predominance.

The necropsy diagnosis was chronic myocarditis, chronic vegetative endocarditis (all valves), chronic fibrinous pericarditis (adherent pericarditis), infarcts of the lung, the spleen and the left kidney, and chronic passive congestion of the viscera.

The gross examination of the heart showed a marked fibrous pericarditis with soft but firm adhesions and some fluid. The heart was greatly enlarged, both

ventricles being thickened. All valves showed small, fresh vegetations. The mitral valve was stenosed. The aortic valve segments were thickened. No gross area of fibrosis was observed in the heart muscle.

The microscopic examination revealed a slight diffuse round cell infiltration in the subpericardial layers of the muscle of both ventricles, apparently an extension of the pericarditis, elsewhere there was no increase of fibrous tissue, and there was no fatty degeneration.

CASE 5—A man, aged 59, was admitted to New York Hospital May 25, 1921, and died June 7. Sixteen months before entering the hospital he had a severe attack of abdominal gas pains. This was followed by recurrences of increasing frequency, with belching and dyspnea on exertion. A cough was present, June 3. The pulse became irregular, and the heart was slightly enlarged, the sounds being distant. The blood pressure was 100 systolic, and 70 diastolic, the urine was normal, and the Wassermann reaction was negative. Clinically,

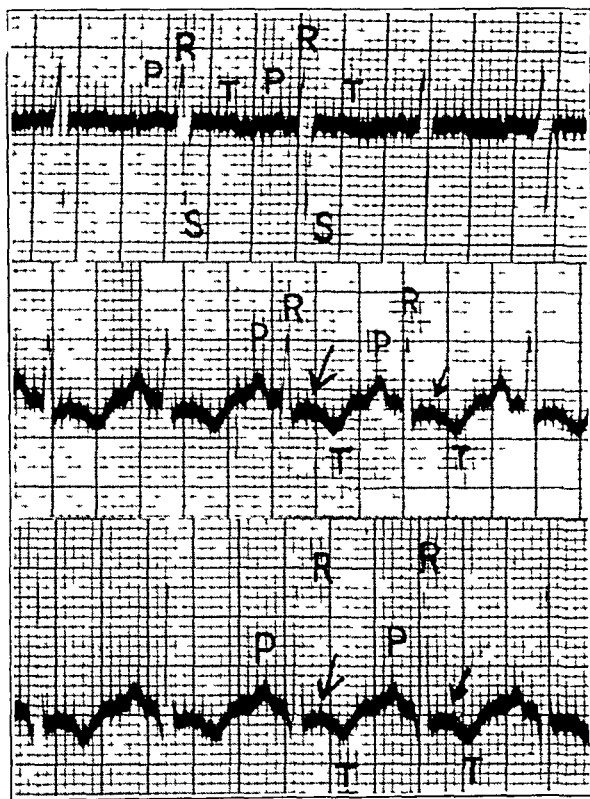


Fig 6 (Case 5) —Q-R-S group, showing right predominance. The T wave is downward in Lead II and has the upward convexity of the R-T interval due to localized coronary narrowing.

the patient was considered to have coronary artery disease with thrombosis of a branch.

The electrocardiogram taken thirteen days before death (Fig 6) showed a right ventricular predominance. The T wave was downward in all three leads, and the upward convexity which preceded T in Leads II and III was like that which has been associated with coronary artery occlusion.

The gross examination of the heart revealed an enlarged, soft, flabby organ, weighing 500 gm. The left ventricle was distinctly dilated and on its posterior surface near the apex was a definite, infarcted area about 9 sq cm in size. The muscle was thinned and pale in this region, on the corresponding endocardial surface it was grayish yellow. The adjacent portion of the septum was similarly involved. The coronaries showed marked thickening. The lumen of the anterior descending branch of the left coronary was occluded by an old thrombus.

Microscopic examination revealed muscle necrosis and fatty degeneration in the region of the infarct, i e, in the septum and in the left ventricle (Fig 7). There were areas of marked fibrous replacement here. In the lateral wall of the left ventricle there also were areas of fibrous replacement, with less marked but very evident fatty degeneration and infiltration. The right ventricle appeared normal, except for a slight increase of connective tissue.

CASE 6—A man, aged 46, who was admitted Sept 5 and died Sept 27, 1919, four weeks before admission had noticed swelling of both limbs, dyspnea on exertion, precordial pain and belching of gas. He had fluid in the right side of the chest ten days after admission. The apex beat was 12 cm to the left

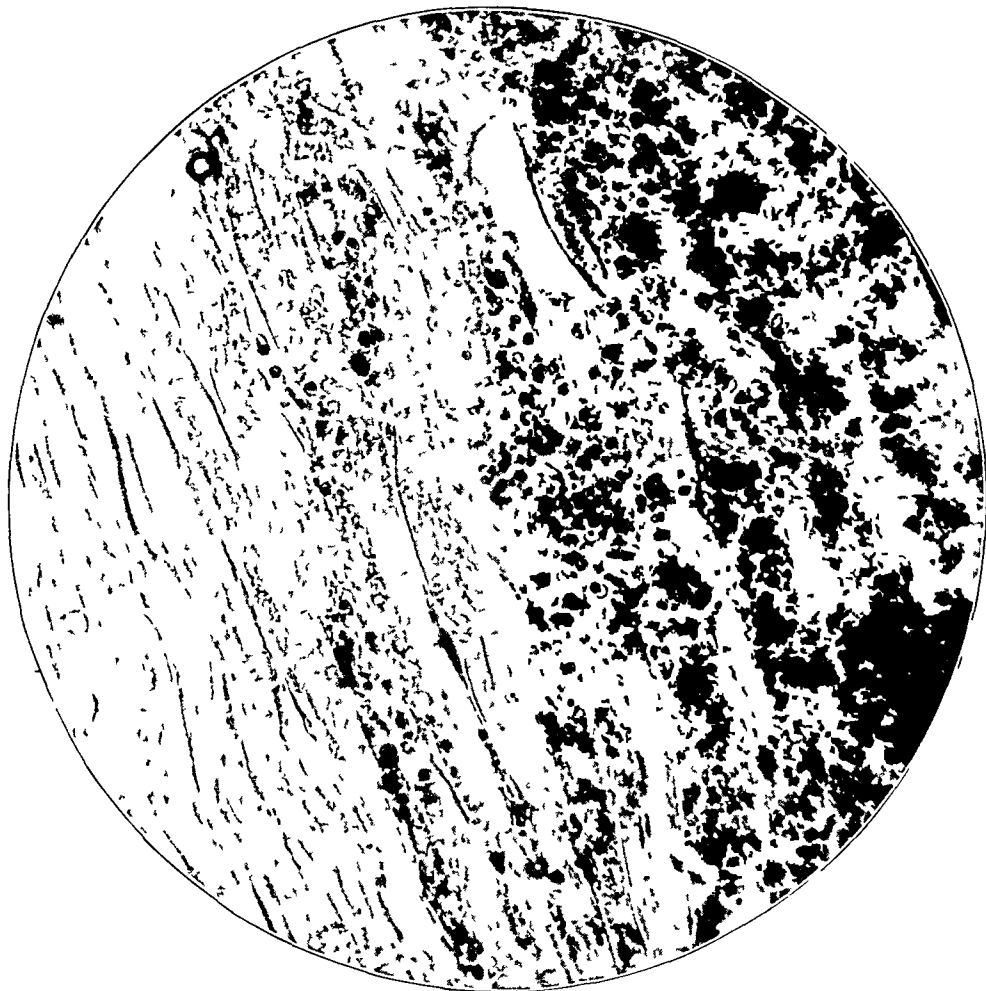


Fig 7 (Case 5)—Fatty degeneration in infarcted area of heart muscle, the fatty granules appear black as scharlach r stain was used

in the fifth space, there were no murmurs. The liver edge was palpable 5 cm below the costal margin. The urine showed albumin, the specific gravity was 1.020, and there were hyaline casts. Phenolsulphonephthalein excretion was 46 per cent in two hours, September 9, 15 per cent, September 19. The blood pressure was 125 systolic, and 85 diastolic. The nonprotein nitrogen was 65 mg.

The electrocardiogram nineteen days before death (Fig 8) showed a Q-R-S group on the borderline of left ventricular predominance. The T wave was downward in Leads I and II (the patient had received scarcely any digitalis, only 90 minims of the tincture in the two days previous to the taking of the electrocardiogram). The excursions of the Q-R-S group were small, only 6 mm.



Fig 8 (Case 6) —Downward T waves in Leads I and II, voltage of Q-R-S group rather low

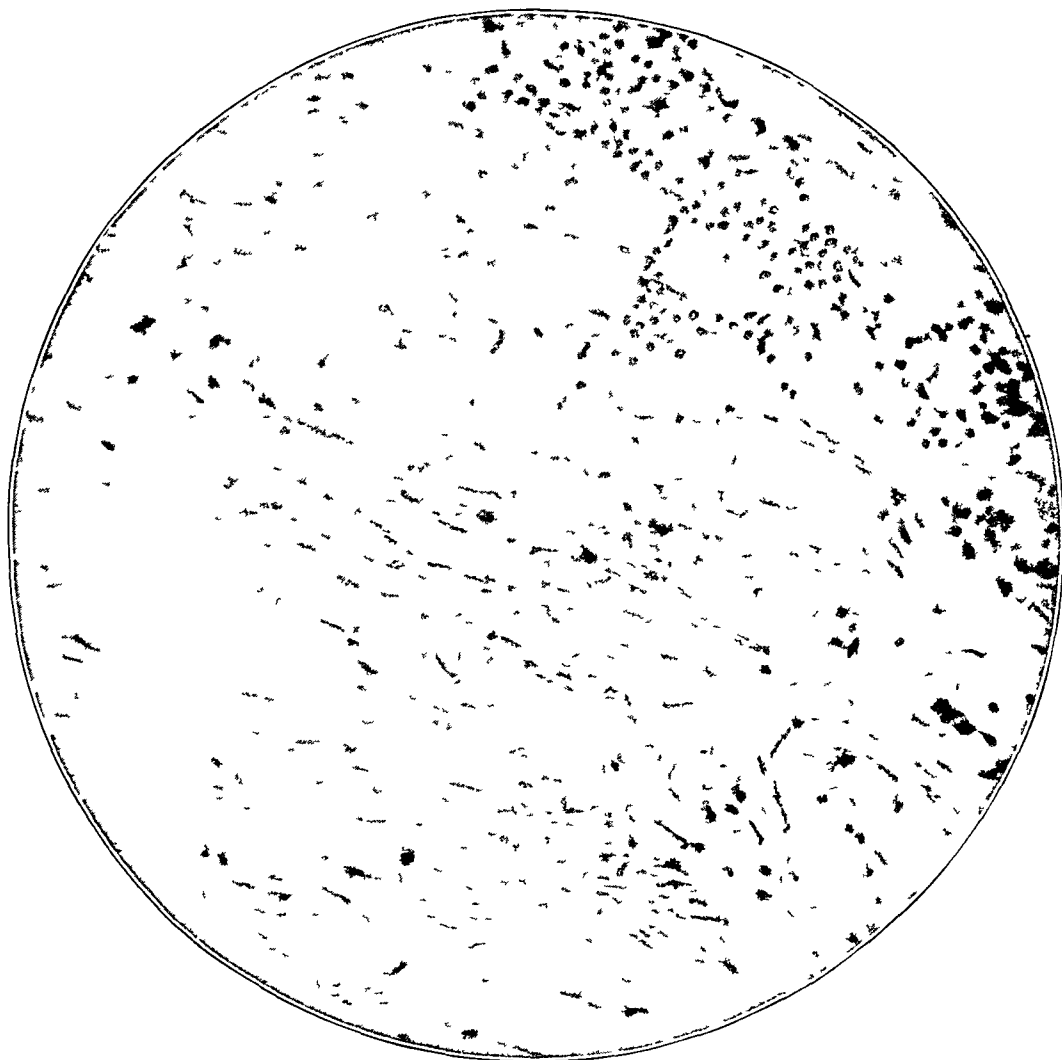


Fig 9 (Case 6) —Section just beneath the pericardium, the subpericardial fat being visible at the top of the picture, marked increase of interstitial connective tissue, subpericardial tissue contains many round cells

The necropsy diagnosis was acute dilatation of the heart, chronic myocarditis, atheroma of the aorta, lung infarct, serofibrinous pleurisy, chronic parenchymatous nephritis, chronic interstitial nephritis, and chronic passive congestion of liver

The gross examination of the heart showed that it was much enlarged, weighing 875 gm. The wall of the right ventricle was thickened, but the left was thinned and small gray areas were scattered throughout it. All the valves were normal. The coronaries showed atheroma, which was marked in the left and for 3 cm this artery was almost completely obliterated by firm calcareous deposits on its walls. The aorta showed many atheromatous patches, most numerous about the coronary orifices and for 4 cm beyond the valve.

Microscopic examination revealed marked connective tissue increase between the muscle bundles of both ventricles, and in some areas the appearance of a fibrous replacement (Fig 9). The subpericardial areolar tissue contained a good many round cells, budding capillaries and fibroblasts. There was no fatty degeneration.

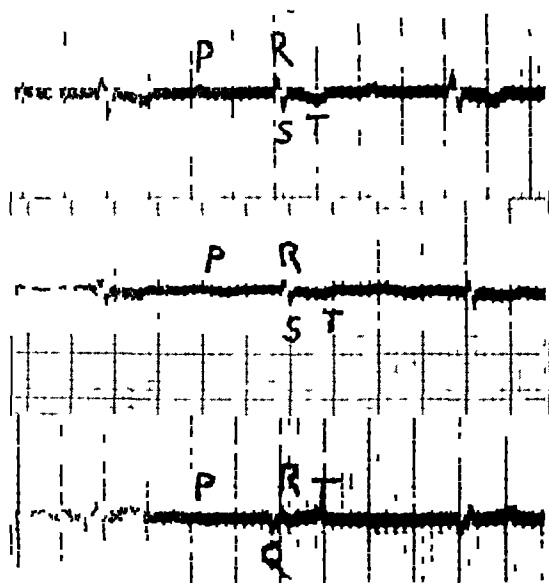


Fig 10 (Case 7)—Record showing prolonged A-V conduction time, P-R measuring 0.32 second, low voltage of Q-R-S group, downward T waves in Leads I and II

CASE 7—A man, aged 57, who was admitted March 3 and died April 25, 1921, entered the hospital with the complaint of dizziness, swelling and pain in the abdomen and legs. He gave a long history of alcoholism and for the last five years had had dyspnea and precordial pain on exertion, rarely accompanied by fainting attacks. The heart was enlarged, 13 cm to the left of the midsternal line in the sixth space and 2 cm to the right in the fourth space. The heart sounds were distant and very poor in quality. Extrasystoles were present with a slow rate of from 50 to 60. The blood pressure was 140 systolic, 90 diastolic. The urine showed a heavy trace of albumin, with hyaline and granular casts, the specific gravity was 1.020. The blood urea was 40 mg per hundred cubic centimeters.

The electrocardiogram nineteen days before death (Fig 10) showed a prolonged auriculoventricular conduction time, 0.4 second. All the waves were very small. The T wave was downward in Leads I and II. During the three days preceding the electrocardiogram, the patient had received 140 minims of tincture of digitalis and 2 ampules of a proprietary preparation of digitalis.

Necropsy findings were chronic parenchymatous nephritis, kidney infarcts, general arteriosclerosis, chronic myocarditis (replacement fibrosis), hypertrophy of the heart, liver congestion, and chronic perisplenitis

The gross examination of the heart showed a considerable increase of fatty tissue on the surface of the organ. The heart was much enlarged. The ventricular walls appeared normal but thinned, and there were no areas of fibrosis. The valves were negative, except very slight thickening of the edge of the mitral valve. The coronaries were markedly thickened and calcified and narrowed throughout.

The microscopic examination of the heart revealed considerable connective tissue replacement in the region of the left apex and also in the right ventricle. The septum showed a moderate degree of fibrous infiltration. There were a few

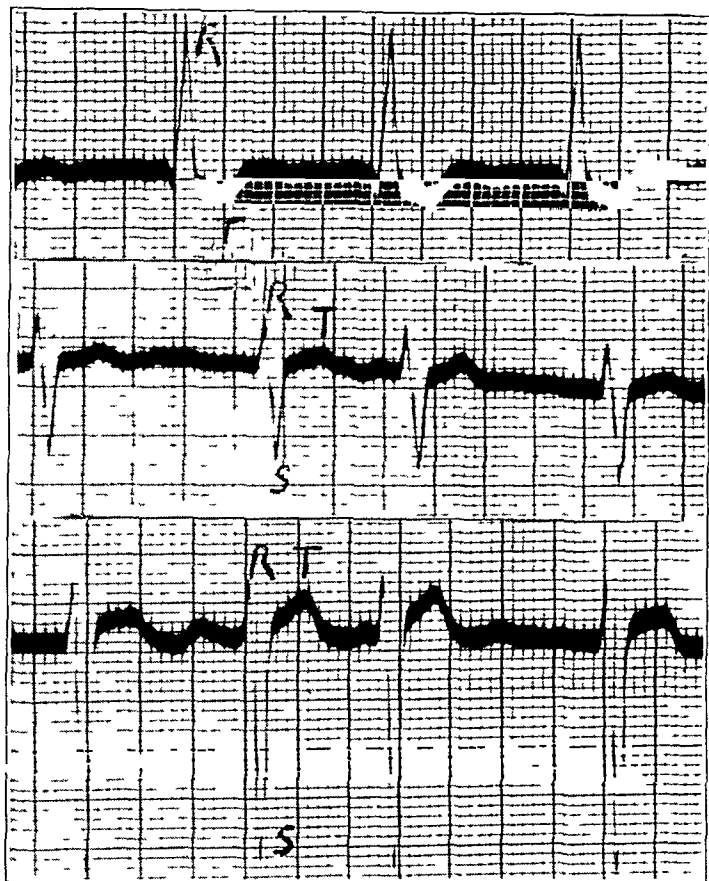


Fig 11 (Case 8) —Auricular fibrillation, the Q-R-S group is abnormally wide and with notching or slurring in each lead, T is downward in Lead I

small round cell foci in the pericardial surface of the left ventricle and, rarely, in the muscle itself. No fatty degeneration was present.

CASE 8—A man, aged 61, who was admitted March 28 and discharged April 19, 1919, had had a doubtful history of tuberculosis at 21. He had had "heart trouble" for twenty-five years and swelling of limbs for nine months previous to admission, when he showed edema of the lower extremities, coughing spells and dyspnea. His heart was enlarged, 14 cm to the left in the seventh space, the heart action was regular. The blood pressure was 130 systolic, and 70 diastolic. The nonprotein nitrogen was 43 mg. The urine showed a faint trace of albumin. The phenolsulphonephthalein output was 33 per cent in two hours. The patient was treated with digitalis and discharged somewhat improved, but was readmitted with edema, cough and dyspnea, May 27, and died June 28.

The electrocardiogram six days before death (Fig 11) showed auricular fibrillation and left ventricular predominance. The Q-R-S group had a duration of 0.12 second and notching in three leads. The T wave was downward in Lead I (possibly explained by the patient's digitalization, which was considerable, about 3½ ounces (104 c.c.) of the tincture having been given in the twenty-five days before the electrocardiogram was taken).

The necropsy diagnosis was general arteriosclerosis, chronic myocarditis, coronary arteriosclerosis, hypertrophy and dilatation of the heart, and chronic passive congestion.

The gross examination of the heart showed that it was markedly enlarged, weighing 640 gm, with numerous small areas of fibrosis in the left ventricle. At the apex the wall was thinned and consisted almost wholly of fibrotic tissue with calcific deposits. The inner surface of this tissue had an attached thrombus.

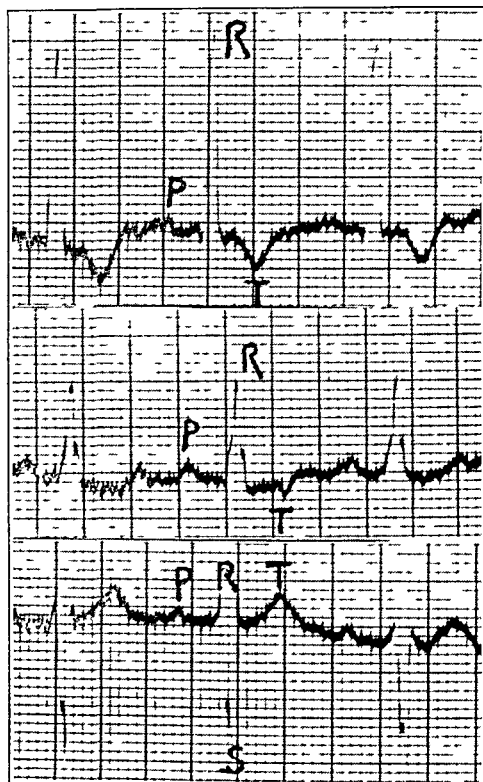


Fig 12 (Case 9)—Record showing abnormally wide Q-R-S group (0.12 second) and notching or slurring in each lead, downward T wave in Leads I and II.

The endocardium showed a patchy sclerosis, especially marked in the apical and anterior part of the septum. The right ventricle, including the endocardium, appeared normal. There was marked atheroma of both coronaries, especially the left, the anterior descending branch being almost obliterated. The valves were practically negative.

Microscopic examination revealed a marked increase in the interstitial connective tissue in the left ventricle while in the right ventricle, where it was only slight, the walls of many of the blood vessels were thickened and occasionally obliterated. There was no fatty degeneration.

CASE 9—A man, aged 52, who was admitted Feb 10 and discharged Feb 22, 1920, was readmitted April 28 and died May 21. There had been a gradual onset of shortness of breath, anorexia, dyspnea and orthopnea after an attack of influenza in February, 1919. Edema developed during the second admission as did

palpitation and vomiting and a bronchopneumonia. The apex beat was 18 cm to the left of the midline in the fifth space. The dulness extended 4 cm to the right in the fourth space. The rate was rapid, and there was a long, blowing systolic murmur at the apex which was transmitted into the axilla. There was liver dulness 4 cm below the costal margin. The blood pressure was 280 systolic, and 170 diastolic on the first admission, 170 systolic and 130 diastolic during the second. The specific gravity of the urine was from 1.010 to 1.020, albumin and granular casts were present. The blood urea was from 60 to 138 mg.

The electrocardiogram twenty-eight days before death (Fig. 12) showed a wide Q-R-S group with notching or slurring in all three leads. Left ventricular predominance was indicated. The T wave was downward in Lead I and zero in Lead II (the patient had received 480 minims of tincture of digitalis for one week and then 20 minims every day for the two weeks previous to the time the record was taken).

The necropsy findings were chronic interstitial nephritis, hypertrophy of the heart, general arteriosclerosis, chronic passive congestion of the liver and kidneys, bronchopneumonia, gangrene of the lung, and chronic pleurisy.

The gross examination of the heart revealed a much enlarged organ, weighing 740 gm. Both ventricles were considerably hypertrophied. All the valves were normal. The coronaries showed extensive atheromatous plaques but no narrowing of the lumen. The endocardium of the left ventricle was much thickened, particularly on the septum, and the endocardium of the right ventricle also was thickened.

The microscopic examination revealed a slight degree of fibrous tissue infiltration throughout the heart muscle, so slight that it could scarcely be considered abnormal. The endocardium was considerably thickened. A portion of the left bundle branch was seen in the section from the septum and seemed quite normal at that level. No fatty degeneration was present.

CASE 10—A man, aged 70, between March 20, 1919, and his death, April 22, 1920, had five admissions to the New York Hospital, each time with the diagnosis of chronic interstitial nephritis and chronic myocarditis. Since 1913 the patient had had "heart and kidney trouble." He had swelling of the legs, precordial pain, dyspnea on exertion, cough, difficulty in urination and nocturia from three to four times a night. The heart rapidly enlarged from 9 cm to the left of the midsternal line in the fourth space, in May, 1919, to 14 cm in the sixth space on the last admission. There was a blowing systolic murmur at the apex, and a short systolic murmur at the aortic area. Edema of the penis, scrotum and legs was present. The heart action was totally irregular, and the liver was enlarged. The urine showed a faint trace of albumin on the first admission, and later a heavy trace, with hyaline casts, the specific gravity was 1.020. The blood pressure ranged from 140 systolic, 60 diastolic, to 160 systolic, 80 diastolic, and reached 200 systolic, 80 diastolic, on his last admission. The nonprotein nitrogen was 64 mg.

The electrocardiogram nine days before death (Fig. 13) showed abnormal ventricular complexes suggesting a partial bundle branch lesion.

At necropsy the diagnosis was chronic interstitial nephritis, chronic cardiac valvular disease, chronic myocarditis (replacement fibrosis), cirrhosis of the liver, chronic passive congestion of the liver and spleen, general arteriosclerosis, and chronic prostatitis.

The gross examination of the heart showed a greatly hypertrophied and dilated organ, weighing 575 gm, with the mitral valves thickened along the edge and the aortic leaflets thickened and fused. The muscle of the left ventricle was thinned out toward the apex. The coronaries were tortuous and stiff, but not occluded, and there was endocardial thickening in the right ventricle between the anterior and the posterior papillary muscles, and in the left ventricle over the lower part of the septum.

The microscopic examination revealed a diffuse connective tissue growth between the cells, especially marked in the left ventricle, and also a fair number of dense fibrous patches in the left ventricle (Fig 14) No fatty degeneration was present

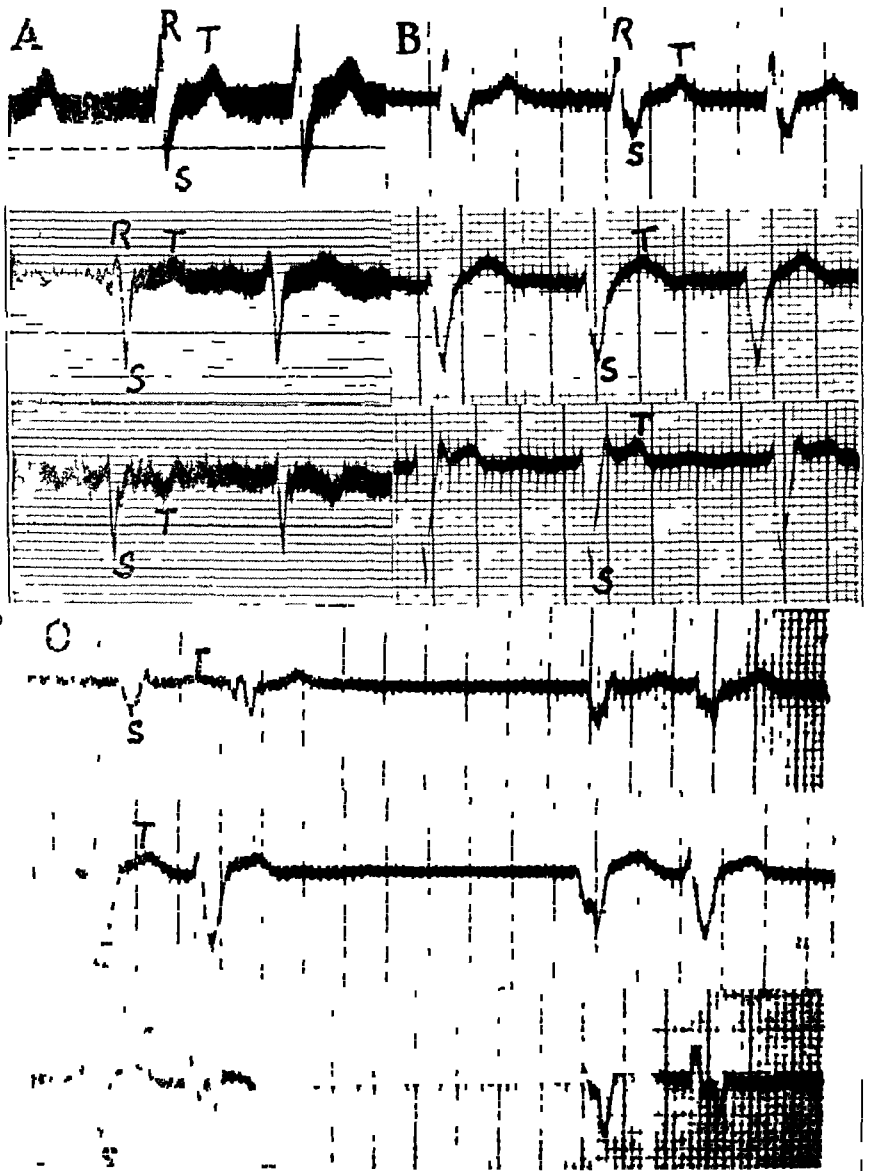


Fig 13 (Case 10) —Auricular fibrillation in all records, *A*, record of December, 1915, showing an unusual Q-R-S group with deep S in all three leads, *B*, record of December, 1919, the ventricular complex now indicating bundle branch block and *C*, record of April 13, 1920, showing complete heart block with ventricular premature beats. The ventricular complexes of the rhythmic beats indicate bundle branch block.

CASE 11—A man, aged 53, had complained of weakness for two years since an attack of pleurisy, with effusion, and shortness of breath commencing six weeks before admission to the hospital, June 2, 1920. There was a history of an old chancre, and the patient complained of a nonproductive cough, precordial pain, dyspnea, orthopnea, and edema of the legs. Physical examination showed

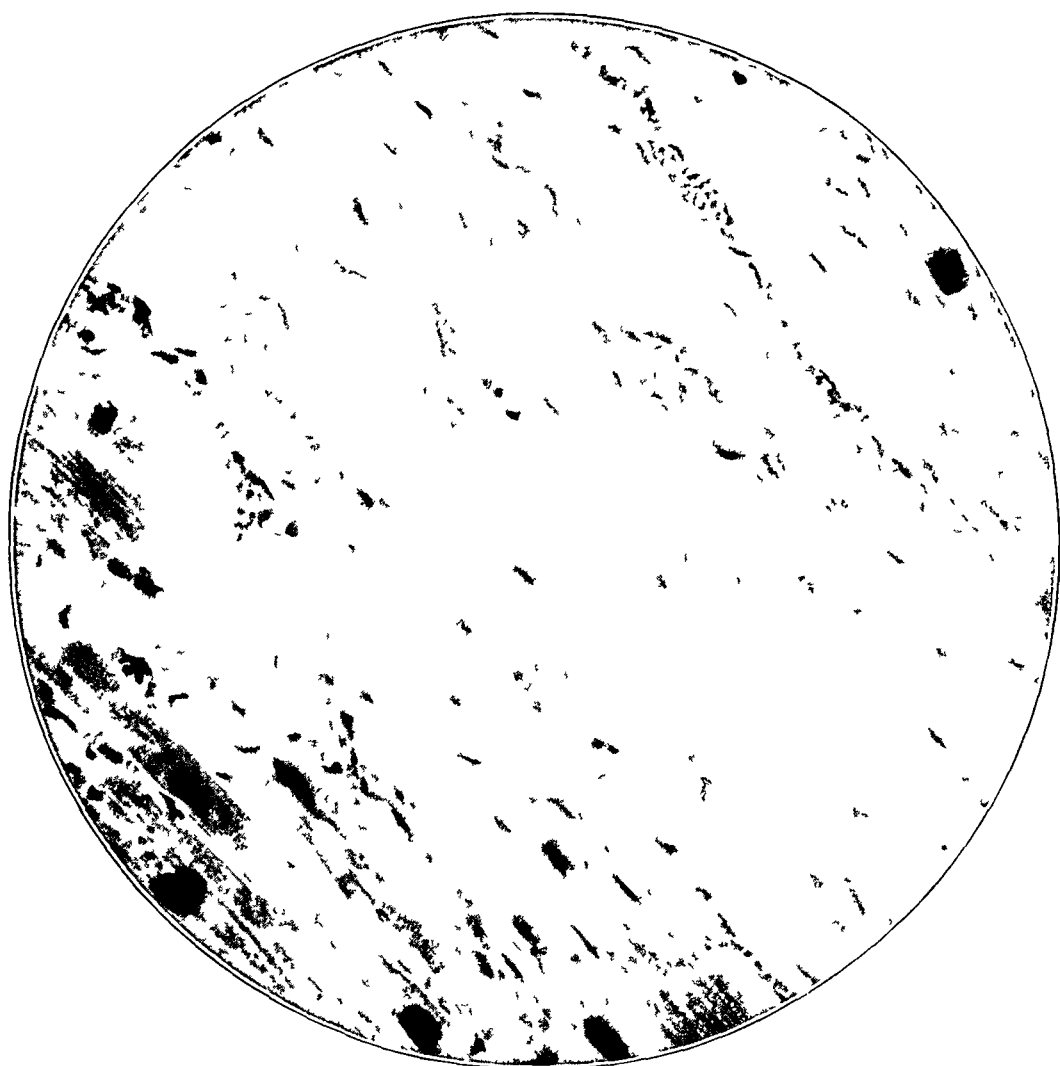


Fig 14 (Case 10) —Dense patch of fibrous tissue in ventricular wall replacement fibrosis

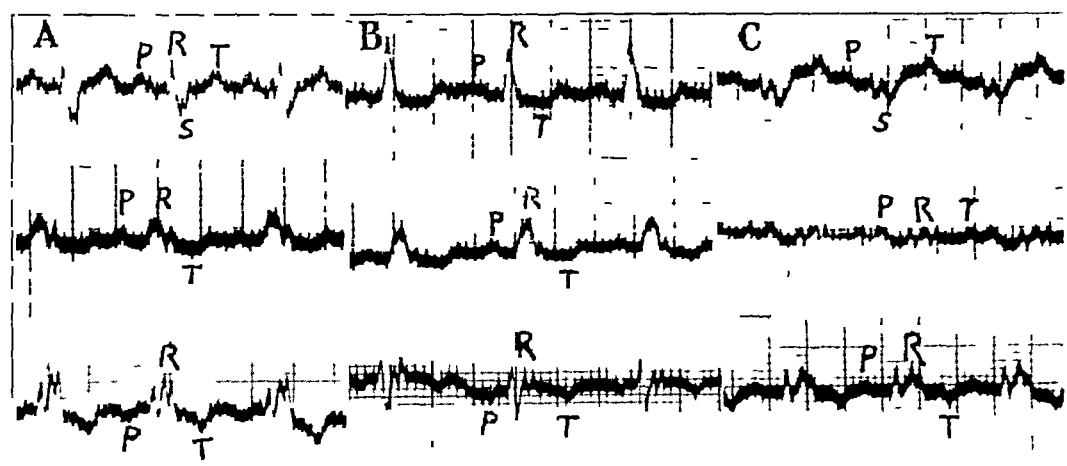


Fig 15 (Case 11) —*A*, record of June 21, of the type associated with arborization block, *B*, record of August 11, less typical of arborization block, and *C*, record of September 30, the last record and quite typical of arborization block. All of these records show sinus rhythm

the heart 14 cm to the left in the sixth space. The sounds were irregular, extrasystoles and a low pitched systolic murmur were heard in the mitral area. The liver was palpable down to the umbilicus. The patient's chest was tapped repeatedly for fluid. The blood pressure was 130 systolic, 80 diastolic. The urine contained albumin, red blood corpuscles, and granular and epithelial casts, the specific gravity was 1.020.

The electrocardiogram taken one day before death (Fig 15 C) showed a small Q-R-S group considerably notched and abnormally wide. The T wave was inverted in Leads II and III, but the patient had received no digitalis in two weeks. The electrocardiogram was of the type associated with arborization block.

The patient died, Oct 1, 1920, four months after admission. At necropsy the diagnosis was chronic interstitial nephritis, chronic valvular disease, hypertrophy of the heart, syphilis of the aorta, chronic passive congestion of the lungs, liver and spleen, and infarcts of the lungs.

The gross examination of the heart showed pericardial fluid and fibrin. The heart was large, weighing 475 gm, and the mitral valve was thickened and sclerosed. The muscle was soft and flabby. There was slight atheroma of the coronaries, the endocardium was normal.

Microscopic examination revealed a considerable degree of fibrous replacement through the heart, especially marked in the left ventricle. No fatty degeneration was present.

COMMENT

In the preliminary report¹ we considered that the first four of these patients had no significant abnormalities of the ventricular waves. The abnormal T waves in the first two cases were ascribed to the digitalis the patient had received.⁷ This was probably the cause, still it is possible that the T wave may have been inverted in Leads I and II before the digitalis was given, so we cannot be certain that there was not a significant T wave abnormality in the records of these patients. The Q-R-S group, however, was normal in both these records.

Case 3 is an example of normal ventricular waves with little or no muscle abnormality. This practically normal ventricular muscle in the presence of evident valvular disease and a probably diseased auriculo-ventricular bundle also is of especial interest.

Patient 4 was considered to have normal Q-R-S waves in spite of the slightly prolonged duration, i.e., 0.12 second instead of 0.1. The heart was extremely large and the thickened wall of the left ventricle would require more time for the spread of the excitation process. For this reason a prolonged Q-R-S interval in this hypertrophied heart was considered normal. Further study of this case indicates that it is more likely that the prolongation of the Q-R-S group was not due to the size of the heart. Records taken, Dec 27, 1920, Jan 8, 1921, and January 25, had a Q-R-S group with a duration of 0.1 second, whereas that of Feb 5, 1921, was the record discussed in the preliminary report. The heart was already greatly hypertrophied, January 25, and it could scarcely

7 Cohn, A. E., Fraser, F. R., and Jamieson, R. A. The Influence of Digitalis on the T Wave of the Human Electrocardiogram, *J. Exper. Med.* **21** 593, 1915.

have increased enough more in the eleven days before February 5 to have caused this change in the duration of the Q-R-S group. As a matter of fact the pericarditis noted at necropsy developed during this period and we now believe that the inflammatory invasion found in the outer ventricular layers was the cause of the delay in the spreading of the excitation and the prolongation of the Q-R-S group.⁸

Patient 5 had an infarct of the heart muscle on the posterior surface of the left ventricle, due to occlusion of the anterior descending branch of the left coronary artery. The electrocardiogram presented the peculiarity of the T wave which is often seen with coronary occlusion of rather recent date.⁹

The ventricular waves of Cases 6 and 7 have small excursions of the Q-R-S group and downward T waves in Leads I and II. Both hearts evidenced thinning of the wall of the left ventricle and, on microscopic examination, fibrous tissue infiltration between the muscle fibers, in areas a denser fibrous tissue had the appearance of replacement fibrosis. The coronary arteries of both these patients were markedly diseased and calcified in areas and the lumina were diffusely narrowed, in places almost closed. The myocardial changes were probably the result of the deficient blood supply. (The downward T waves of Case 7 might have been due to digitals but the amount of the drug was scarcely sufficient to produce the change.)

Patient 8, whose record showed a large notched Q-R-S group and in Lead I a downward T wave, showed disease of the character and distribution that has been associated with "arborization block" curves.⁴ The record of this patient does not show the typical "arborization block" features.

8 The records taken, February 5, before and after removal of 500 c.c. of pericardial fluid afford an interesting example of the effect of such fluid on the electrocardiogram and on the position of the heart.

	P R Interval	Maximum Excursion Q-R-S	Angle Alpha for R ₂	Maximum Excursion T Wave	Angle Alpha for T ₂
Before tapping	0 20	8 5 mm	70	2 0 mm	60
After tapping	0 20	10 0 mm	76	2 5 mm	66

The lower voltage in the presence of the fluid may be due to short-circuiting of the electric current within the pericardial sac. The changes in the angle alpha (the angle between the horizontal and the axis of electric potential of the heart at any given moment) is probably due to the shifting of the position of the heart by the fluid. A similar decrease in the voltage has often been observed with pericardial effusion in the course of routine clinical records, but this is the only case that I have observed directly before and after tapping.—H. E. B. P.

9 Pardee, H. E. B. An Electrocardiographic Sign of Coronary Artery Occlusion, *Arch Int Med* **26** 244 (Aug.) 1920. Smith, F. M. Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *Arch Int Med* **32** 497 (Oct.) 1923.

In this connection a case reported by Drury¹⁰ is important, for he, too, found a pathologic picture similar to ours and the electrocardiogram of his case failed to show any arborization block features. It is evident from these two hearts that the special pathology often associated with the arborization block features of the electrocardiogram may occur without causing the special electrocardiographic changes.¹¹

The electrocardiographic curves of Case 11 had a small, widened and notched Q-R-S group and presented all the criteria of arborization block. The heart, however, did not have the typical pathologic findings which have been associated with that condition, e. g., no closure of the anterior descending branch of the left coronary artery, in fact, the atheroma here was slight. Nor were the fibrous changes accentuated in the endocardial or subendocardial layers, they were rather diffusely distributed but more marked in the left ventricle.

Case 11 shows that all the electrocardiographic criteria of arborization block may be present without the expected pathologic findings. Two of the cases reported by Oppenheimer and Rothschild⁴ were also in this category. These authors emphasized the predominance of the pathologic changes in the endocardial and subendocardial layers as compared with the outer two thirds of the ventricular muscle. They considered that the former situation favored an involvement of the finer ramifications of the auriculoventricular conduction system. This endocardial and subendocardial distribution of the pathologic changes was evident in our Case 8 and in Drury's reported case, neither of which gave the typical curves.

Evidently the association of this special pathology and the special electrocardiographic features of "arborization block" is not a constant one, though the electrocardiographic changes have not occurred except in the presence of a considerable disease. It seems that a diffuse muscle disease, by causing an abnormal spreading of the contraction stimulus, may produce the notched and widened Q-R-S complex and prevent the development of the normal voltage of these waves, so that their amplitude is low. Such a diffuse disease will most commonly be secondary to coronary disease, though it may be primary, owing to rheumatic or syphilitic infection.

Though we believe that the low voltage of the waves in arborization block curves is usually the result of a diffuse disease, yet Case 8 is an exception to this association, having diffuse disease and large waves.

10 Drury, A. N. Arborization Block, Heart 8 23 (Feb.) 1921.

11 Drury's curve had only slightly abnormal ventricular waves. The Q-R-S was not notched and had a duration of 0.1 second. The waves had the following values: $R_1 = 6$ mm, $S_1 = 0$, $R_2 = 6$ mm, $S_2 = 3$ mm, $R_3 = 5$ mm, $S_3 = 5$ mm. The T wave was upward in Leads I and II. $T_1 = 0.7$ mm, $T_2 = 0.7$ mm, $T_3 = 0$.

A later record of his case was suggestive of right bundle branch block but without notching of Q-R-S.

The record of Case 9 presented a notching of the Q-R-S group with inversion of T_1 and T_2 while the ventricular muscle itself showed a diffuse but slight increase of connective tissue. The endocardium of both ventricles was thickened, especially on the septal surface of the left ventricle near the apex. Here then is a case in which the terminal ramifications of the bundle branch tissue may have been interfered with by the thickened endocardium, causing an abnormal spreading of the contraction stimulus. The abnormal T wave may be due to the same cause, for if the distribution of the contraction stimulus is sufficiently abnormal the T wave will be changed.¹² This case emphasizes another variety of electrocardiographic change which may result from an interference with the spreading of the contraction stimulus within the ventricles. It seems that we are unable to determine from the presence of a notched Q-R-S and an abnormal T wave whether there is a diffusely diseased ventricular muscle (Case 8) or endocardial fibrosis (Case 9), or whether both factors are present.

Case 10 illustrates another result of disease interfering with the spreading of the contraction. The earlier records, as in Diury's case, are not striking in their abnormality.¹³ Records taken in September, 1919, in December, 1919, and April 13, 1920, shortly before death, showed the wide and notched Q-R-S of bundle branch block but did not have the typical direction of Q-R-S and T for either a right or a left bundle branch lesion.

This heart was the seat of extensive changes in the muscle, especially marked in the left ventricle where there were silvery patches of fibrosis throughout. Moreover, there was a fibrous thickening of the endocardium at the apical part of the septum in the left ventricle and in the region between the papillary muscles of the right ventricle. In either of these positions the branches of the auriculoventricular bundle may have been involved in the fibrosis. Here we have an extensively damaged muscle and possibly a damaged conduction system to account for the changes in the electrocardiogram.

Since all the patients of this series died of cardiac failure there is a certain clinical interest in the fact that two of the four hearts with valvular disease had quite a normal ventricular muscle, and only one of the four had much abnormality of the muscle. On the other hand

12 Wilson, F. N., and Herrmann, G. R. An Experimental Study of Incomplete Bundle Branch Block, *Heart* 8: 229 (May) 1921.

13 The record of December, 1915, was abnormal both in having a well developed S_1 with left ventricular predominance and in the notching of S_3 . A record of May, 1916, showing left predominance but with a small S_1 , would probably pass as normal. These records from a known case of disease suggest that if S_1 is present in records of left ventricular predominance it may have to be considered abnormal.

of the six arteriosclerotic hearts, all had a definitely abnormal muscle. The patients with valvular disease, it appears, died before the muscle was sufficiently affected to appear abnormal under the microscope so that the valvular damage must have been the chief factor in the heart failure. In the group with normal valves the muscle disease was extensive and was the evident cause of death in all but one case in which the patient, who had high blood pressure and uremia, died of bronchopneumonia (Case 9).

SUMMARY AND CONCLUSIONS

The outstanding feature of this study seems to us to be the variability of the electrocardiographic abnormality when extensive chronic lesions of the ventricular muscle are present. Cases 6, 7, 8, 10, 11 and that of Drury all showed extensive fibrosis of the ventricular muscle with most varied effects on the ventricular waves of the electrocardiogram. Drury's case and our Case 8 had the results of long standing occlusion of the descending branch of the left coronary artery, in effect an old scar, and in neither case was there a special electrocardiographic peculiarity. Case 6 showed a narrowing of this artery but not an occlusion and showed still different ventricular waves.

Even low voltage, which is usually associated with extensive lesions (Cases 6, 7, 10 and 11), was not found in Case 8, so that it is apparently not a constant result of widespread disease.

There has been apparently no specific relation between the type of electrocardiographic abnormality and the pathologic process found in the heart. There have been curves of arborization block which have not been associated with the special pathologic findings (Case 11) and, on the other hand, the special pathologic findings have appeared without these special curves (Case 8 and Drury's case).

The special T wave abnormality said to be associated with recent coronary artery closure has been again demonstrated in such a case (Case 5).

Pericarditis with effusion (Case 4) may possibly decrease the voltage of electrocardiographic waves and may prolong the Q-R-S duration if the inflammation extends into the ventricular muscle.

We have seen other necropsies since this series was first observed and we have not yet seen normal ventricular waves when more than a very slight abnormality of the ventricular muscle was demonstrable, nor have we seen extensive disease with normal waves.

In other words, an abnormal electrocardiogram of any of the types we have described is indicative of a diseased heart while a normal electrocardiogram is a sign of a fairly healthy muscle.

We believe that disease of the ventricular muscle plays the dominant rôle in producing abnormalities of the electrocardiographic curve by

causing an abnormal development of the electrical product of the contraction. If the conduction tissue becomes involved in disease of the endocardium this also may cause changes in the curve by causing an abnormal spreading of the contraction. Each of these factors will have a variable importance in any given case.

A COMPARISON OF ACUTE RHEUMATIC AND SUBACUTE BACTERIAL ENDOCARDITIS *

B J CLAWSON, M D

AND

E T BELL, M D

MINNEAPOLIS

A typical case of subacute bacterial endocarditis is characterized clinically by a septic temperature, physical signs of valvular heart disease, evidence of embolic processes (petechiae, embolic glomerulonephritis, etc.), and a positive blood culture (streptococcus). There is often a secondary anemia and moderate enlargement of the spleen, and death usually results within two years. On the other hand, the characteristic features of acute rheumatic endocarditis are acute arthritis, fever, evidence of valvular heart disease, absence of embolic processes, and a tendency to recover with or without a valve defect. Typical instances are therefore easily distinguished clinically, but there are many cases in which the diagnosis is uncertain.

The transition from the acute rheumatic to the subacute bacterial type may be so gradual that it is impossible to say where the one ends and the other begins. The following history illustrates such a case.

REPORT OF CASE

A white girl, aged 23, became ill, Jan 15, 1924, with swelling, stiffness and tenderness of the joints (elbows, wrists, knees and ankles), fever and chills, dyspnea, palpitation and weakness. After two weeks in bed she returned to work, but was obliged to rest every few days. Sometimes she noticed edema in the ankles at the end of a day. She continued to have chills and fever, especially in the forenoon, and gradually grew weaker. She was admitted to the hospital, Feb 18, 1924.

Seven years before admission she had an attack similar to this one except that it was more severe. At that time practically all the joints of the extremities were involved, and she was confined to bed for a month.

Physical examination, February 18, showed an enlarged heart with a systolic murmur at the apex. A friction rub could be heard at the right border of the sternum. The joints were swollen and tender. Two days after admission, petechiae were found on both extremities and the spleen was palpable for the first time. The hemoglobin on admission was 80 per cent. It gradually decreased until a few days before death, when it was 38 per cent. The number of red blood cells was reduced gradually from 4,700,000 to 2,000,000. The leukocytes ranged from 6,000 to 4,000. Two days after admission many red blood cells were found in the urine, and they continued to be present during the remainder of the course of the disease. The temperature ranged from 99 to 103. She gradually grew weaker and died, April 6, 1924. *Streptococcus viridans* was isolated in pure culture from the blood at different times before death and at necropsy. Necropsy revealed a typical anatomic case of subacute bacterial endocarditis with infarcts of the spleen and kidneys and embolic glomerulonephritis.

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It is particularly difficult to distinguish a so-called mild case of subacute bacterial endocarditis from the rheumatic form. With improved methods of isolating bacteria from the blood a high percentage of positive cultures may be obtained from cases of typical rheumatic endocarditis. Apparently, this may be the explanation of the increasing number of reports of recovery from subacute bacterial endocarditis. Not infrequently the original clinical diagnosis is changed from rheumatic to subacute bacterial endocarditis or vice versa to fit the subsequent progress of the case. From a study of a large number of cases one gets the impression that these two forms of endocarditis represent mild and severe degrees of the same infection. Miller¹ expressed this idea in speaking of mild cases of subacute bacterial endocarditis when he said that formerly he would have diagnosed such cases rheumatic endocarditis. Biggs² states that, clinically, many cases of subacute bacterial endocarditis cannot be distinguished from rheumatic endocarditis.

In this paper the division of fatal cases of endocarditis into the acute rheumatic and the subacute bacterial types is based on the clinical course and the gross anatomic character of the vegetations—whether small, smooth and hard (rheumatic) or large, soft and villous (subacute bacterial). A comparison of the two types is made in respect to (1) the blood picture, (2) the gross and microscopic anatomic characteristics, and (3) the bacteriology.

Eighty cases of subacute bacterial endocarditis that came to necropsy are compared with thirty-five cases of rheumatic endocarditis, eighteen of which came to necropsy. The remaining seventeen are typical cases of rheumatic endocarditis clinically, and *Streptococcus viridans* was isolated from all of them.

BLOOD PICTURE

Leukopenia and Leukocytosis—A leukopenia may occur in subacute bacterial endocarditis, and this fact probably explains the occasional confusion with influenza, typhoid fever, malaria and incipient tuberculosis. The total leukocyte count has been suggested as a means of differentiating subacute bacterial from rheumatic endocarditis. The data available in our cases are analyzed in Table 1. It will be noted that a leukopenia (below 6,000) is present in four of the subacute bacterial group but not in any of the rheumatic cases. A definite leukocytosis (above 15,000) is found in 50 per cent of the rheumatic and in 39 per cent of the subacute bacterial cases. On the whole the

1 Miller Joseph, in discussion of Kilgore, E. S. Arrhythmia of Auricular Fibrillation, abstr., J. A. M. A. **82** 1722 (May 24) 1924.

2 Biggs, A. D. Prognosis of Chronic Infectious Endocarditis, Arch. Int. Med. **35** 402 (March) 1925.

leukocyte count is slightly lower in the subacute bacterial than in the rheumatic endocarditis, but it is of little value in differentiating the two types

Anemia—Anemia of the secondary type has been mentioned by various workers as characteristic of subacute bacterial endocarditis and has been considered of value in differentiating it from acute rheumatic endocarditis. A hemoglobin determination of nineteen of the thirty-five cases of acute rheumatic endocarditis is recorded. In only six cases does the hemoglobin drop below 80 per cent, and in only one is it below 60 per cent (Table 1). On the other hand only 20 per cent of the cases of subacute bacterial endocarditis have a hemoglobin percentage of more than 80 per cent, and in 33 per cent the hemoglobin is below 60. The reduction in number of red blood cells corresponds

TABLE 1—*Comparison of Rheumatic and Subacute Bacterial Endocarditis as Regards the Leukocyte Count, Hemoglobin and Erythrocyte Count*

	Acute Rheumatic Type		Subacute Bacterial Type	
	Number	Per Cent	Number	Per Cent
Leukocytes				
15 to 25 thousand per c mm	10	50	19	39
10 to 15 thousand per c mm	5	25	15	31
8 to 10 thousand per c mm	3	15	5	10
6 to 8 thousand per c mm	2	10	6	12
Below 6 thousand per c mm	0	0	4	8
Total	20		49	
Hemoglobin				
80 to 100 per cent	13	68	9	20
60 to 79 per cent	5	26	21	47
Below 60 per cent	1	5	15	33
Total	19		45	
Erythrocytes				
4.5 to 5 million per c mm	11	65	13	30
3.5 to 4.5 million per c mm	5	29	15	35
Below 3.5 million per c mm	1	6	15	35
Total	17		43	

with the reduction in the hemoglobin (Table 1). In the subacute bacterial type, the degree of anemia increases with the progress of the disease. A severe anemia points strongly to the subacute form, but there may be only a moderate anemia in early stages.

ANATOMIC CHARACTERISTICS

Valves Involved—The involvement of valves in order of frequency in the eighteen rheumatic cases is: The mitral alone, eight (44.5 per cent), the aortic alone, none, the mitral and aortic, two (11 per cent), the mitral and tricuspid, three (16.5 per cent), the aortic and tricuspid, three (16.5 per cent), the mitral, aortic and tricuspid, one (5.5 per cent), and the mitral, aortic, tricuspid and pulmonary, one (5.5 per cent) (Table 2). In the eighty cases of subacute bacterial endocarditis,

the valves involved are the mitral alone, thirty (37.5 per cent), the aortic alone, twenty-three (29 per cent), and the mitral and aortic, nineteen (24 per cent). Other combinations are rare. The number of acute rheumatic cases is too small for a satisfactory statistical comparison, but assuming that practically all old healed valves are produced by previous rheumatic infections, it is of interest to note that the three chief combinations of valvular involvement are about the same in rheumatic and in subacute bacterial cases. The order of frequency, which varies slightly from that in the subacute bacterial, is the aortic and mitral, forty-seven (41 per cent), the mitral, thirty-four (29.5 per cent), and the aortic, twenty-one (18 per cent). In either group the aortic and mitral are the only valves involved to any extent, although the involvement of the tricuspid in the acute rheumatic cases is relatively frequent. It is important to observe that the involvement of the aortic

TABLE 2—*Frequency of Involvement of the Various Valves in Acute Rheumatic and Subacute Bacterial Endocarditis and in Old Valve Defects*

	Acute Rheumatic Endocarditis, 18 Cases		Subacute Bacterial Endocarditis, 80 Cases		Old Valve Defects, 115 Cases	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Mitral	8	44.5	30	37.5	34	29.5
Aortic	0	0	23	29	21	18
Tricuspid	0	0	3	4	0	0
Mitral and aortic	2	11	19	24	47	41
Mitral and tricuspid	3	16.5	2	2.5	4	3.5
Aortic and tricuspid	3	16.5	1	1	0	0
Mitral, aortic and tricuspid	1	5.5	2	2.5	7	6
Mitral, aortic, tricuspid, pulmonary	1	5.5	0	0	1	0.9
Total mitral	15	83	53	66	93	81
Total aortic	7	39	45	56	76	66
Total tricuspid	8	44	8	10	12	10
Total pulmonary	1	5.5	0	0	1	0.9

alone is of not infrequent occurrence. The order of involvement of valves offers nothing of differential significance between subacute bacterial and acute rheumatic endocarditis.

Gross Vegetations—In endocarditis immediately associated with acute rheumatic fever (rheumatic endocarditis, simple verrucous endocarditis), the heart valves on gross examination show small, smooth, globular nodules at the points of contact of the leaflets and on their free margins. Usually, these vegetations are not extensive enough to interfere seriously with the function of the valve.

The chief lesions found on the valves in subacute bacterial endocarditis are soft villous vegetations. These vegetations do not have the smooth surfaces found on the vegetations in acute rheumatic endocarditis. The consistency and size of the subacute bacterial vegetations make it easily possible for particles to break loose into the blood stream and produce the embolic processes so commonly found in subacute bacterial endocarditis.

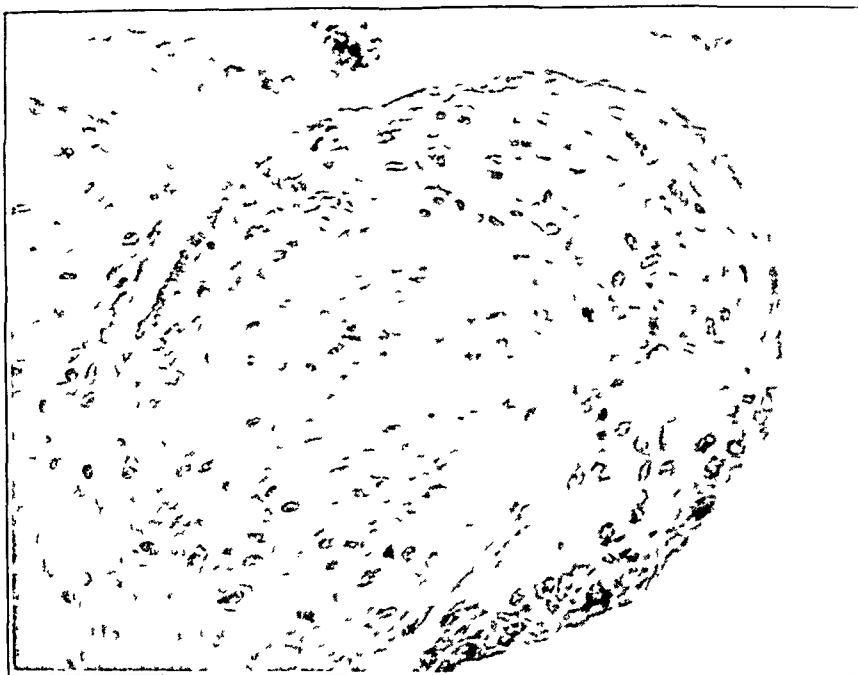


Fig 1—Early rheumatic vegetation

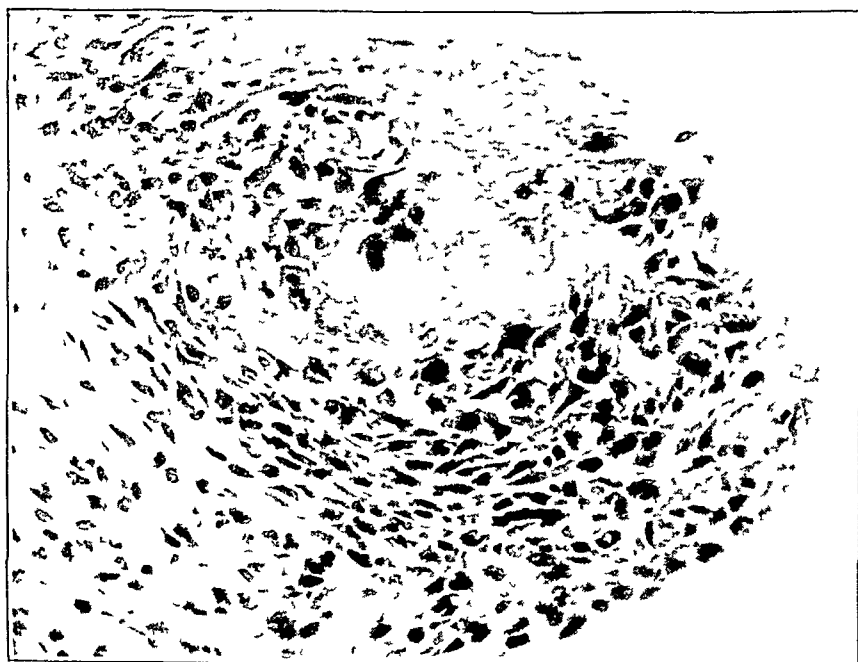


Fig 2—Early rheumatic vegetation showing a small thrombotic mass and rupture of endothelium

Vegetations characteristic of the rheumatic type may generally be found on the same cusps with the vegetations of the subacute bacterial type. Acute rheumatic vegetations may be present on the cusps on one valve while on another there may be subacute bacterial lesions.

Microscopic Appearance of Vegetations—Microscopically, the rheumatic vegetations show inflammation, chiefly proliferative in character, but containing a few polymorphonuclear leukocytes and many large cells having one or more vesicular nuclei similar to those found in the Aschoff nodules in the myocardium. Small masses of fibrin, a little serous exudate, and sometimes areas of necrosis are present (Figs 1 and 2). The inflammatory process begins within the substance of the leaflet and extends to the surface, frequently causing desquamation of the endothelium. A small amount of thrombotic material is generally found, but it is not sufficient to cause a gross roughening or the detachment of particles with the production of embolic processes (Fig 3).

TABLE 3—*Mural Endocarditis, Pericarditis and Enlargement of the Spleen in Acute Rheumatic and Subacute Bacterial Endocarditis and in Old Valve Defects*

	Acute Rheumatic Endocarditis, 18 Cases		Subacute Bacterial Endocarditis, 80 Cases		Old Valve Defects, 115 Cases	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Auricle	4	40	9	11	0	0
Ventricle	0	0	17	21	0	0
Auricle and ventricle	0	0	6	7.5	0	0
Total mural endocardial involvement	4*	40	32	40	0	0
Pericarditis	13	72	18	22.5	21	18
Spleen 450 gm. or more	1	5.5	19	24		

* Ten were examined

The condition of the valve is in reality a valvulitis as well as an endocarditis. This inflammatory condition of the cusps is typical in the eighteen cases of acute rheumatic endocarditis coming to necropsy.

Microscopically, the leaflets in the thirty cases of subacute bacterial endocarditis studied showed a valvulitis similar to that found in the leaflets in acute rheumatic endocarditis (Figs 4 and 5). On the endocardial edge of the inflammatory area of the subacute bacterial valve, there is a platelet thrombus which is more extensive than that found in the acute rheumatic valve. As a rule, masses of streptococci are found in the thrombotic mass in the subacute bacterial type, but few or none are found in the active proliferative area. The condition of the valve in subacute bacterial endocarditis is essentially a valvulitis mostly proliferative in character, as in acute rheumatic endocarditis, but in addition having an adherent infected thrombotic mass. This addition of the larger infected thrombotic mass distinguishes the subacute bacterial vegetation from the acute rheumatic vegetation and seems to be a difference in degree of involvement.

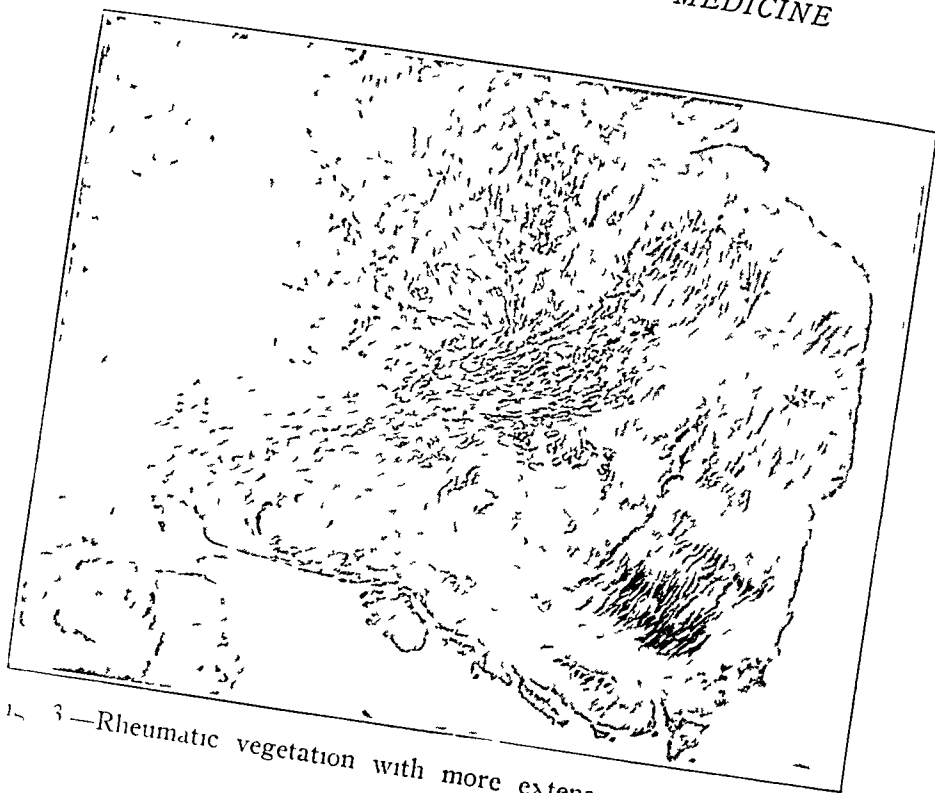


Fig. 3—Rheumatic vegetation with more extensive thrombotic mass

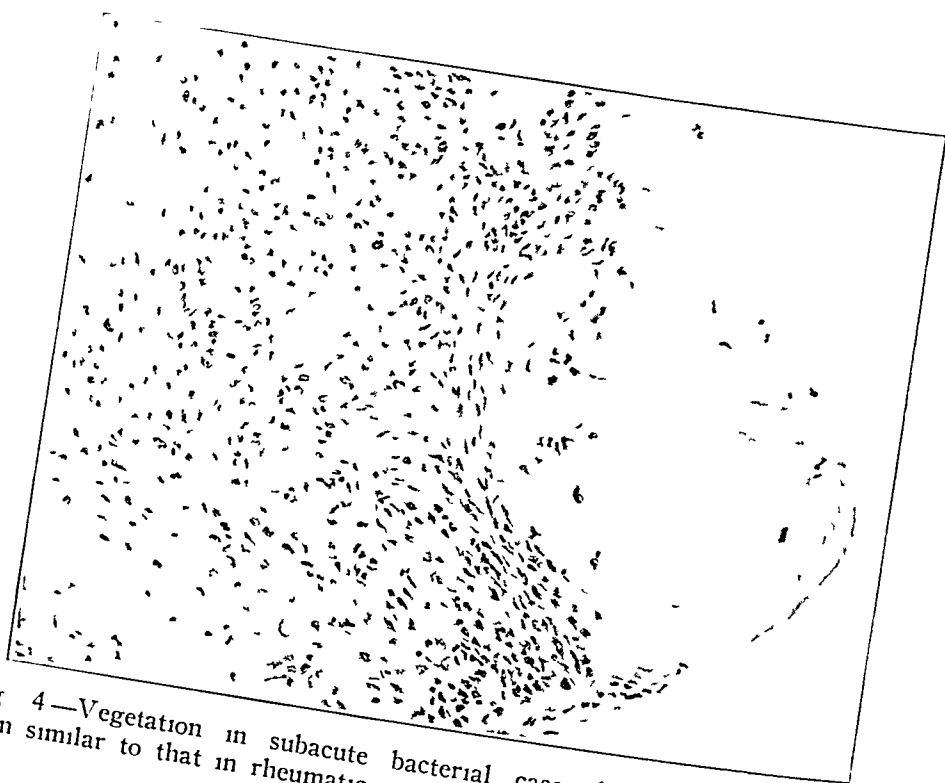


Fig. 4—Vegetation in subacute bacterial case showing an inflammatory reaction similar to that in rheumatic vegetations

Mural Endocardium—The involvement of the mural endocardium has been described as a characteristic of subacute bacterial endocarditis. MacCallum³ states that he not infrequently finds a thickening of the auricles with a fibrinous exudate over the thickened area in acute rheumatic hearts. We have found auricular involvement corresponding to the lesions described by MacCallum in 40 per cent of the rheumatic cases examined (Table 3). The structure of these mural endocardial lesions was similar to the rheumatic vegetations. In the eighty cases of subacute bacterial endocarditis, the auricular endocardium alone was involved in nine (11 per cent), the ventricular endocardium alone in seventeen (21 per cent), and both the auricle and the ventricle in six (7.5 per cent). In all, there was involvement of the mural endocardium in thirty-two (40 per cent). The mural endocardial involvement in subacute bacterial endocarditis shows lesions corresponding to subacute bacterial vegetations. This involvement is believed by Murray⁴ to result, in most cases, from direct extension from the valve and from the repeated contact of the infected vegetation with the mural endo-

TABLE 4—*Myocardial Lesions Associated with the Different Forms of Endocarditis*

Type	Number Examined	Myocarditis of All Types		Aschoff Nodules		Proliferative Lesions		Exudative Lesions	
		Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Acute rheumatic	18	18	100	14	78	18	100	0	0
Subacute bacterial	61	14	23	7	11.5	12	86	0	14
Experimental streptococcal	13	10	77	2	15	13	100	0	0

cardium. The character of the lesions in the auricular endocardium in rheumatic cases suggests, however, that at least some of the mural endocardial lesions may be extensions from subendocardial infections. Involvement of the mural endocardium is found in both types of endocarditis and is therefore not a differential feature.

Myocardium.—Acute myocarditis other than that found with acute rheumatic endocarditis is rare. The type of inflammation illustrated by the Aschoff nodule or the rheumatic subcutaneous nodule has in general come to be considered a specific type of inflammation characteristic of the rheumatic virus. Libman⁵ found these bodies in eighteen (32.1 per cent) of fifty-six cases of rheumatic endocarditis. Thayer⁶ found acute myocarditis in twenty-two (88 per cent) of twenty-five cases of acute rheumatic endocarditis. Aschoff nodules were present in twenty-one (87.5 per cent) of twenty-four cases examined.

3 MacCallum, W. G. Bull. Johns Hopkins Hosp. **35**: 329 (Oct.) 1924.

4 Murray, L. M. Ann. Clin. Med. **1**: 18 (July) 1922.

5 Libman, E. Characterization of Various Forms of Endocarditis, J. A. M. A. **80**: 813 (March 24) 1923.

6 Thayer, W. S. Bull. Johns Hopkins Hosp. **36**: 99 (Feb.) 1925.

In the eighteen cases of acute rheumatic endocarditis in our series coming to necropsy, myocarditis was present in all (100 per cent) (Table 4). The Aschoff nodule was found in fourteen (78 per cent). In seven of the sixty-one cases of subacute bacterial endocarditis examined (11.5 per cent), the Aschoff nodule was present. In two of these, the tricuspid valve showed typical rheumatic vegetations, while subacute bacterial vegetations were present on other valves. Two cases were typical examples showing a continuous transition from acute rheumatic fever to subacute bacterial endocarditis. The other three cases were in persons in the first and second decades of life. The course of the disease was short and in two there was a history of rheumatism.

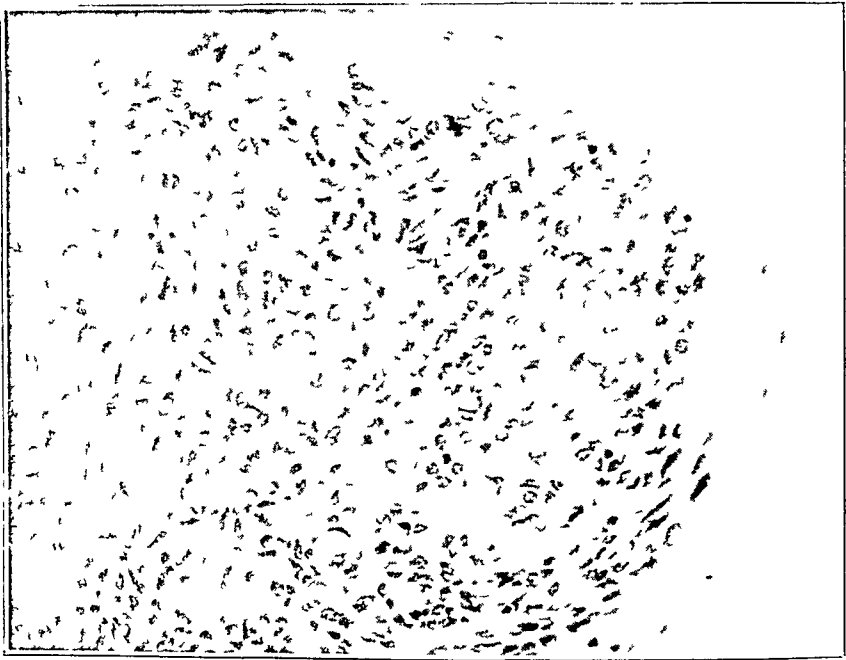


Fig. 5—Vegetation in subacute bacterial case showing an inflammatory reaction similar to that in rheumatic vegetations

Definite active inflammation was found in fourteen (23 per cent) of the sixty-one cases of subacute bacterial endocarditis (Table 4). In all but two of the fourteen the inflammation was proliferative in character, with some large mononuclear and multinucleated cells. In these two cases, polymorphonuclear leukocytes were found which suggested that the lesions were embolic in character.

It is obvious that the type of inflammation represented by the Aschoff nodule is of more frequent occurrence in acute rheumatic endocarditis. The necropsy reports of such hearts are relatively small as it is unusual for death to occur at this stage. If the Aschoff nodule represents a specific type of reaction to the rheumatic virus, then the nodules evidently disappear rapidly since they are so infrequently found.

in cases of subacute bacterial endocarditis (11.5 per cent) and in cases of healed defective valves (8.5 per cent) which are known to have had rheumatic infections

Pericarditis—The greater frequency of pericarditis with acute rheumatic endocarditis than with subacute bacterial endocarditis has been emphasized by various workers. This is true if we base our statistics on the necropsy findings in the subacute bacterial and rheumatic types. Acute rheumatic endocarditis, however, usually does not result in death and when it does pericarditis is one of the usual causes of death. Statistics concerning the relative frequency of pericarditis can be obtained more accurately if we compare subacute bacterial endocarditis with the cases in which death is due to old valve defects, since there is a general agreement that defective valves for the most part result from previous rheumatic infections. In the eighty cases of subacute bacterial endocarditis, pericarditis was found in eighteen (22.5 per cent) (Table 3). It was present in thirteen (72 per cent) of the eighteen cases of acute rheumatic endocarditis. In the 115 cases of healed defective valves pericarditis was present in twenty-one (18 per cent). It is seen that the frequency of pericarditis in cases of acute rheumatic endocarditis coming to necropsy is high. It is also noted that the frequency of pericarditis in subacute bacterial endocarditis and in cases with healed defective valves coincides closely. The comparison is not exact since 59 per cent of the subacute bacterial group apparently developed on old healed defective valves (probably of rheumatic origin), but the comparison does show that the frequency of pericarditis with rheumatic endocarditis is not high. It appears from these considerations that an associated pericarditis should not be considered a differential feature between the subacute bacterial and the rheumatic types.

Embolic Processes—It may be safely said that embolic phenomena never occur in acute rheumatic endocarditis. In rare cases in heavy infections, petechiae may be noted but, as Gibson⁷ pointed out, too much diagnostic importance must not be placed on petechiae even when they are found in recurrent crops for they may be present in nonembolic pathologic conditions such as septicemia.

In the eighty cases of subacute bacterial endocarditis, sixty-five (81.25 per cent) showed the presence of embolic processes (Table 5). These were distributed as follows: petechiae, thirty (37.5 per cent), infarcts of spleen, thirty-nine (48.75 per cent), infarcts of kidney, thirty-two (40 per cent), and infarcts of the brain, thirteen (16.25 per cent). If the embolic processes are considered on the basis of infarcts of spleen, kidneys and brain, there were fifty-one (63.75 per cent) which showed embolic phenomena. In the eighteen cases of rheumatic

⁷ Gibson, A. G. Brit. M. J. **2**: 308 (Aug. 28) 1920.

endocarditis, petechiae were reported in two (11 per cent) There were no other embolic phenomena Embolic glomerulonephritis was found in forty-two (58 per cent) of seventy-two cases of subacute bacterial endocarditis, but in none of the eighteen acute rheumatic cases The demonstration of embolic processes either clinically or anatomically affords a definite differentiation from rheumatic endocarditis, but it is to be remembered that this feature depends on the structure of the valvular vegetations, i e, whether they are soft and villous or firm and smooth It is probably a difference in degree rather than in the type of lesion

Enlarged Spleen—The spleen was found to weigh 450 gm or more in nineteen (24 per cent) of the subacute bacterial group and in one (5.5 per cent) of the acute rheumatic group (Table 3) Therefore, a definitely enlarged spleen suggests the subacute form of endocarditis, but the absence of this finding is of little value in the differential diagnosis The increased size of the spleen may be due in part to passive

TABLE 5—*Embolic Phenomena Associated with Endocarditis*

	Acute Rheumatic Endocarditis, 18 Cases		Subacute Bacterial Endocarditis, 80 Cases	
	Number	Per Cent	Number	Per Cent
Petechiae	2	11	30	37.5
Infarct of spleen	0	0	39	49
Infarct of kidney	0	0	32	40
Infarct of brain	0	0	13	16
Embolic glomerulonephritis	0	0	42*	58
Total embolic processes	2	11	65	80
Infection of spleen, kidney or brain	0	0	51	64

* Seventy-two were examined

congestion, but seems to be caused largely by hyperplasia resulting from infection.⁸

BACTERIOLOGY

The work of many investigators, Swift and Kinsella,⁹ Horder,¹⁰ Libman,¹¹ Gow,¹² Curschmann,¹³ Boyd,¹⁴ Murray and Loughheed¹⁵ and others, has demonstrated that subacute bacterial endocarditis is caused by streptococci, usually the viridans strains, but there is still no general agreement concerning the etiology of acute rheumatic endocarditis

8 Arnett, I. H. *Am J M Sc* **163** 590 (April) 1922

9 Swift, H. F., and Kinsella, R. A. *Bacteriologic Studies in Rheumatic Fever*, *Arch Int Med* **19** 381 (March) 1917

10 Horder, T. J. *Brit M J* **2** 301 (Aug. 28) 1920

11 Libman, E. *Brit M J* **2** 304 (Aug. 28) 1920

12 Gow, A. E. *Brit M J* **2** 307 (Aug. 28) 1920

13 Curschmann, H. *Munchen med Wchnschr* **69** 419 (March 24) 1922

14 Boyd, F. D. *Edinburgh M J* **27** 129 (Sept.) 1921

15 Murray, L. M., and Loughheed, G. W. *Canad M A J* **11** 666 (Sept) 1921

Streptococci have been isolated from the blood, the joints or the pericardial exudate in cases of acute rheumatic fever by Westphal, Wassermann and Malkoff,¹⁶ Poynton and Paine,¹⁷ Beaton and Walker,¹⁸ Walker and Ryffel,¹⁹ Loeb,²⁰ Camisa,²¹ Beattie and Yates,²² Collins,²³ Rosenow,²⁴ LaFetra,²⁵ Swift and Kinsella,⁹ Quigley²⁶ and others

Positive bacteriologic findings are recorded in thirty-two of the eighty cases of subacute bacterial endocarditis (Table 6). Of these strains five were hemolytic, twenty-two belonged to the viridans group, and five were not tested on blood agar. In eleven of the eighteen cases of acute rheumatic endocarditis coming to necropsy, an effort was made to isolate organisms. In nine a streptococcus was found. In five of these cases, it was found in the blood, in two, in the pericardial fluid, in one, in the pericardial fluid and spleen, and in one, in the blood before death and in the pericardial fluid at necropsy. In seventeen other cases the organism was isolated from living patients, once from the pericardial fluid, twice from the joints, and fourteen times from the blood. In all, streptococci were isolated in twenty-six cases of acute rheumatic fever and endocarditis. Twenty-four of these

TABLE 6—*Bacteriology*

Type of Endocarditis	Number of Positive Cases	Streptococcus Viridans	Streptococcus Hemolyticus	Action on Blood Not Determined	Blood Before Death	Blood at Necropsy	Pericardial Fluid	Joints
Acute rheumatic	26	24	2	0	15	6	5	2
Subacute bacterial	32	22	5	5	18	14		

strains belonged to the viridans group and two to the hemolytic group. It is seldom possible to recover these organisms in less than ten days of incubation at 37 C.²⁷ It has been our experience that if the blood for culture is taken when the temperature is high the organism can be isolated in more than 50 per cent of the cases.

When compared with eleven of the twenty-five rheumatic strains, three subacute bacterial strains were found to agree in general in morphology, cultural characteristics, immune reactions, and in ability to produce experimental endocarditis in rabbits.²⁷

- 16 Westphal, Wassermann and Malkoff. Berl klin Wchnschr **36** 638, 1899
- 17 Poynton, F. J., and Paine, A. Lancet **2** 861, 1900
- 18 Beaton, R. M., and Walker, E. W. A. Brit M J **1** 237, 1903
- 19 Walker, E. W. A., and Ryffel, J. H. Brit M J **2** 659, 1903
- 20 Loeb, L. M. Arch Int Med **2** 266 (Oct.) 1908
- 21 Camisa, G. Centralbl f Bakteriöl **57** 99, 1910
- 22 Beattie, J. M., and Yates, A. G. J Path & Bacteriol **17** 538, 1912
- 23 Collins, J. R. Brit M J **1** 220, 1913
- 24 Rosenow, E. C. J Infect Dis **14** 61, 1914
- 25 LaFetra, L. E. Arch Pediat **32** 135, 1915
- 26 Quigley, W. J. J Infect Dis **22** 198 (March) 1918
- 27 Clawson, B. J. J Infect Dis **36** 444 (May) 1925

Two groups of organisms were found by agglutination, dilution 1 10,000 (Table 7) Seven rheumatic serums showed fairly uniform agglutination results with the fourteen organisms tested and represented a homogeneous group No agglutination occurred with the remaining rheumatic serums except with their homologous strains These were representatives of a heterogeneous group Three subacute bacterial serums were tested with the same fourteen organisms Two of these serums fell into Group 1 and one into Group 2 Agglutination in high dilutions apparently does not differentiate strains of rheumatic origin from strains of subacute bacterial origin

Tunnichiff ²⁸ found an increased opsonic content for streptococci in the blood of rheumatic patients In the serums of seven cases out of

TABLE 7—Agglutinations, 1 10,000

Serums of Rheumatic Origin	Organisms													
	Rheumatic Origin											Subacute Bacterial Origin		
	1	2	4	5	6	8	9	11	13	16	17	7	15	19
2	+	+	+	+	+	—	+	+	+	+	+	+	+	—
6	+	+	+	+	+	—	+	—	+	+	+	+	+	—
13	+	+	+	+	+	+	+	—	+	+	+	+	+	+
9	+	+	—	+	+	+	—	—	+	—	+	+	+	+
5	+	+	+	+	+	—	+	—	+	—	+	+	+	—
17	+	+	+	+	+	—	+	—	+	—	+	+	+	—
1	+	+	—	+	—	—	+	—	+	+	+	+	+	—
4	—	—	+	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	+	—	—	—	—	—	—	—	—
11	—	—	—	—	—	—	—	+	—	—	—	—	—	—
Serums of Subacute Bacterial Origin														
19	—	—	—	—	—	+	—	—	—	—	—	—	—	+
7	—	+	+	+	+	+	—	—	+	+	+	+	+	—
15	+	+	+	+	+	—	+	+	+	—	+	+	+	—

twelve, she found agglutinins for the same organisms In all of twelve cases of subacute bacterial endocarditis, Kinsella ²⁹ found agglutinins Swift and Kinsella ⁹ were not able to find agglutinins (dilutions, 1 40) in the blood in five cases of rheumatic fever We have tested seven serums from rheumatic fever patients Five showed agglutinins in dilutions of 1 50 These positive serums agglutinated organisms isolated from acute rheumatic fever, chorea and subacute bacterial endocarditis The presence of these agglutinins in the patients' serums suggests the streptococcus as the exciting agent in the etiology of rheumatic fever and also shows a relation between these strains and subacute bacterial strains

²⁸ Tunnichiff, R J Infect Dis 6 346, 1909
²⁹ Kinsella, R A Streptococcus Endocarditis, Arch Int Med 19 367 (March) 1917

When injected into rabbits, nine strains of rheumatic origin and one of subacute bacterial origin produced endocarditis grossly and microscopically similar to human rheumatic endocarditis (Fig 6). One rheumatic strain produced in addition a typical subacute bacterial lesion with embolic processes in the kidney. From what was found in experimental endocarditis and myocarditis there is reason to believe that the myocarditis associated with acute rheumatic endocarditis is caused by streptococci. In ten of the thirteen cases of experimental endocarditis produced in rabbits by injecting streptococci, myocarditis was present (Table 4). The inflammation consisted of diffuse and nodular proliferative lesions with a slight degree of exudation (Fig 7). In some areas a small amount of necrosis was present. The lesions contained



Fig 6—Vegetation in experimental streptococcic endocarditis (rabbit)

large mononuclear and multinucleated cells with vesicular nuclei. Some of the nodular lesions were similar morphologically to Aschoff nodules in cases of human rheumatic carditis (Fig 8).

On the basis of morphology, cultural characteristics, agglutination tests and ability to produce experimental endocarditis, there is a suggestion that streptococci are responsible not only for subacute bacterial endocarditis but for acute rheumatic endocarditis.

Clinically, the two types of endocarditis under discussion were usually distinct but transition forms were occasionally seen. The clinical differences corresponded to the severity of the infection and the structural changes in the valves. Histologic studies of the valve leaflets indicated also that the two forms of endocarditis differ only in the intensity of the inflammatory reaction.

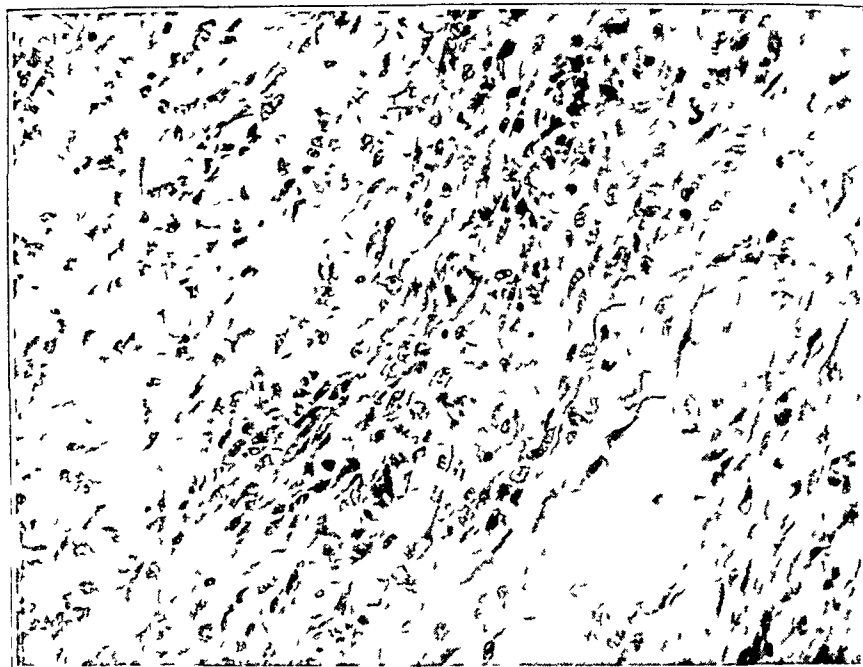


Fig 7—Experimental streptococcic myocarditis (rabbit)

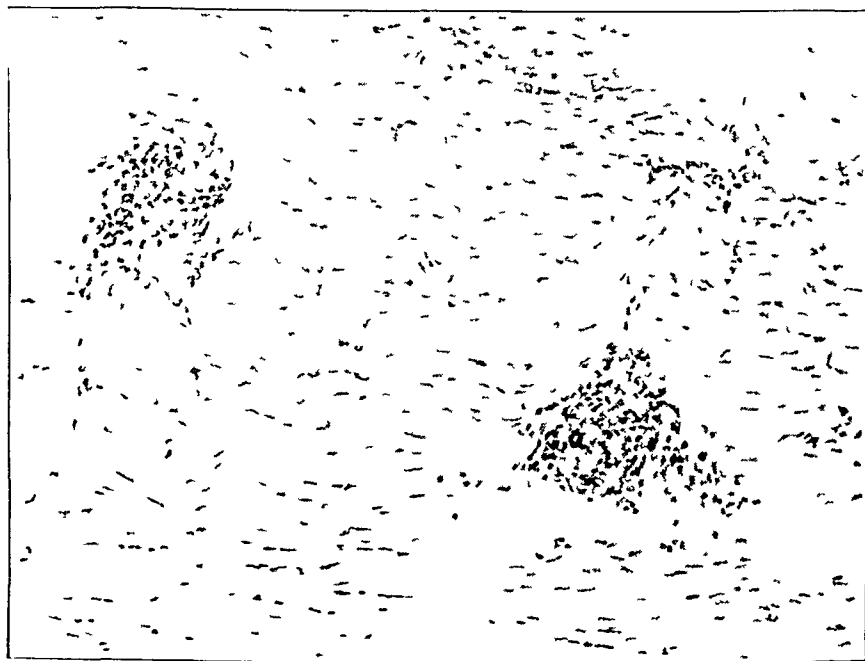


Fig 8—Nodular lesions in the myocardium (rabbit) resembling Aschoff nodules

SUMMARY

The leukocyte count is of little value in differentiating rheumatic from subacute bacterial endocarditis

A severe secondary anemia strongly suggests the subacute bacterial type

The order of frequency of valvular involvement is essentially the same in both forms

In both types there is a proliferative inflammation in the valve, but the thrombus over the infected area is larger and softer in the subacute lesion. The differences are in degree rather than in kind. Typical rheumatic vegetations may be found with subacute vegetations on the same leaflet

Myocarditis is more frequent in the acute rheumatic cases that come to necropsy

Pericarditis seems to occur with practically the same frequency in rheumatic and in subacute bacterial endocarditis

The frequent presence of embolic phenomena in the subacute bacterial type depends on the degree of involvement of the infected valves

Mural endocardial involvement occurs with about the same frequency in both types but is more extensive in the subacute bacterial

The finding of bacteria in the blood stream in endocarditis does not necessarily indicate the presence of the condition clinically recognized as subacute bacterial endocarditis

Experimental endocarditis and myocarditis similar to human rheumatic lesions can be produced in rabbits by injecting streptococci

The streptococci, generally the viridans strains, seem to be responsible for both rheumatic and subacute bacterial endocarditis

WATER METABOLISM †

EDMUND ANDREWS, M D

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Investigators in the field of water metabolism have generally taken it for granted that all the water in the body is fixed by the colloids and electrolytes in a firm combination and that changes in this colloid-water complex must be postulated to account for any variations in the tissue fluid concentrations Fischer,¹ indeed, postulated a "free" and "combined" water in the tissues, but the "free" water, according to his conception, seemed to be merely the superfluous fluid derived from metabolic processes or from ingestion which was promptly excreted

During the course of studies of the so-called dehydration fevers in dogs it was noted that the diuresis produced by injections of equivalent amounts of glucose varied within wide limits and in many instances failed entirely

These injections were made with the Woodyatt pump Merck's "white granular glucose" was used Balcar² injected 36 per cent glucose solution at the rate of 15 gm per kilogram of body weight per hour, using a carefully purified form of glucose In my experiments such concentrations proved toxic, and a lower rate was adopted, 20 per cent glucose solution was injected at the rate of 6 gm per kilogram of body weight per hour The injections were continued for ninety minutes This may explain the failure of other observers to corroborate Woodyatt's results

Detailed studies of the conditions of the dogs were made and many factors which might account for this variation were ruled out The sugar metabolism as shown by the amount of dextrose excreted and by blood sugar determinations before and during the experiments, varied within narrow limits The parallelism of the rise in the blood sugar in different experiments showed that the glycogen reserve and the storage power were not factors

The creatinin, nonprotein nitrogen, urea and cholesterol of the blood were studied together with the normal urinary findings as to albumin, casts, etc, and renal disease as a factor was ruled out

It was noted, however, that the amount of water that it was possible to extract from the body by this means bore a definite relation to the

† From the department of experimental surgery, University of Illinois College of Medicine

1 Fischer, M F Edema and Nephritis, Ed 3, London, John Wiley & Sons, 1921

2 Balcar, J O, Sansum, W D, and Woodyatt, R T Fever and the Water Reserve of the Body, Arch Int Med 24 116 (July) 1919

reaction of the tissues as measured by the plasma carbon dioxide combining power. This was determined by the Van Slyke method. The experiments given here are illustrative.

TABLE 1—*Experiment 17*

A female dog, weighing 12.5 kg, was injected with 20 per cent glucose solution at the rate of 6 gm of glucose per kilogram of body weight per hour				
Time	Intake	Urine	Loss	Loss Per Kilogram
9 55	Injection begun, carbon dioxide combining power, 54			
10 10	90	75		
10 25	181	180		
10 40	273	350	77	6
10 55	365	520	155	12
11 10	456	800	344	27
11 25	547	1,000	453	36
11 40	547	1,075	528	42
12 05	547	1,135	588	47
12 20	547	1,175	628	51
Urine ceased				

TABLE 2—*Experiment 18*

A female dog, weighing 8.5 kg, was injected with 20 per cent glucose solution at the rate of 6 gm of glucose per kilogram of body weight per hour				
Time	Intake	Urine	Loss	Loss Per Kilogram
10 00	Injection begun, carbon dioxide combining power, 46.5			
10 15	71	45		
10 30	142	85		
10 45	213	180		
11 00	285	315	30	4
11 15	356	425	69	7
11 30	427	475	50	6
11 45	427	495	70	8
Urine ceased				

From a series of such experiments it was possible to construct Table 3.

TABLE 3—*Results in Series of Experiments*

Experiment	Carbon Dioxide Combining Power	Loss Per Kilogram
12	44.5	0 (gained 50 cc)
19	45.5	13
13a	46.5	23
18	46.5	8
20	46.6	28
16	49.0	49
14	49.2	56
13	50.0	41
17	54.0	51 plus (some urine lost)

It will be seen from Table 3 that the critical point in the alkali reserve is about 45. Below that level it was not possible to produce any dehydration by the injection of glucose at this rate. As the alkali reserve rose there was a nearly parallel rise in the water loss. For each cubic centimeter of carbon dioxide, approximately 10 cc per kilogram of water is separable from the tissues.

COMMENT

It is not a new concept that water occurs in the tissues in different degrees of combination with the colloids. Fischer¹ postulated a "free" and a "combined" water. These terms are merely relative and probably represent a loose and a firm combination. Hitherto, it has been impossible to make any clear demonstration of this even *in vitro*, but the foregoing experiments not only afford a demonstration *in vivo*, but also a method of measuring the "free" water. For our purposes we may safely assume that the "combined" water cannot be freed by any such means used. The tenacity of the colloid-water compound is too great. The extent to which this method may be said to furnish a quantitative estimation of the "free" water is debatable, but in view of the accuracy with which small variations may be predicted, it is at least valuable as a relative measure when other factors are eliminated.

It is a reasonable deduction that the level of 45 of the carbon dioxide combining power is the point at which all the water in the body is "combined" or fixed. At least that is the level at which its affinity for the colloids in the tissues is greater than its affinity for the glucose. At higher levels there is in addition a certain amount of water in a looser combination, a water reserve.

This concept enables us to explain certain clinical phenomena which Fischer's reasoning will not.

It is well known that in suppression of urine from various causes the intravenous injection of Fischer's solution (sodium carbonate, 1.4 per cent, sodium chloride, 1 per cent) will at times produce a flow of urine, but failure is perhaps more common. This can now be explained on the basis that the urinary flow will not be resumed until the carbon dioxide combining power is 45 or higher. The amount of alkali necessary to do this is tremendously in excess of that usually administered. Of course no amount of fluid given in extreme cases can be adequate because the degree of acidity of the tissues in severe acidosis may be sufficient to increase the hydrophilic action of the colloids to such an extent that the body would swell to twice its normal size if water were available. Illustrative experiments are given in Tables 4 to 6.

TABLE 4—*Experiment 32*

Female dog, weighing 10 kg., given no food or water for thirty-six hours

9 20 a m Catheterized, heart blood taken, carbon dioxide combining power, 27.9

9 35 a m Urine only a few drops

9 35 a m Given 0.5 gm. of sodium bicarbonate (10 per cent solution) intravenously

9 50 a m Urine only a few drops heart blood taken, carbon dioxide combining power, 35

In Experiment 32 the amount of alkali administered was insufficient to raise the alkali reserve above the critical level and no diuresis ensued.

In Experiment 30 the alkali given was enough to raise the carbon dioxid combining power above 45 and prompt diuresis ensued

Experiment 13 afforded a curious confirmation of this concept

The dose of alkali administered in Experiment 13 was far too large and was rapidly fatal, but in the few minutes in which the dog survived 15 c c of urine was passed and the edema of the lungs was striking in its extent. After much had spilled on the floor, a beaker placed under the dog's head collected 50 c c of frothy mucus in a few minutes. The sudden overalkalinization of the tissues freed such a tremendous amount of fluid that there was no time to absorb it into the circulating mediums, and that part freed in the lungs found its way into the bronchi. This occurred in spite of the fact that the dog had already lost a maximal amount of water. This was repeated in subsequent experiments and it appears that if the amount of alkali necessary to

TABLE 5—Experiment 30

Female dog, weighing 9 kg, given no food or water for forty eight hours	
2 30 p m	Catheterized, heart blood taken, carbon dioxid combining power, 42
2 45 p m	Only a few drops of urine
2 45 p m	0.5 gm of sodium bicarbonate (10 per cent solution) intravenously
3 00 p m	15 c c of urine, heart blood taken, carbon dioxid combining power, 47

TABLE 6—Experiment 13

Female dog, weighing 10.4 kg, injected with 20 per cent glucose solution at rate of 6 gm per kilogram of body weight per hour for ninety minutes, animal lost 23 c c per kilogram. Flow of urine stopped in 95 minutes.	
Solution of 15 c c of 10 per cent sodium bicarbonate injected into the right femoral vein.	
Animal died in six minutes from edema of the lungs, in these six minutes 15 c c of urine passed.	

bring an acid animal suddenly to the critical level is administered suddenly, edema of the lungs is the rule. In the cases in which there is not an undue amount of fluid held by the colloids, that is, in which the alkali reserve is already above the critical level, a much larger dose of alkali is easily tolerated.

BODY WEIGHT

According to the usual conceptions of the chemistry of colloids, the slightest variations in the reactions of the tissues should bring about changes in body weight. It is well known that this is not true clinically. There is a considerable range in which no such changes occur. That this range in the dog is that between the alkali reserve levels of 45 and 54 will be seen from the experiments in Tables 7 and 8.

In Experiment 21 the dog was near the critical level and the acid administered was sufficient to bring the carbon dioxid combining power well below it, water was retained, causing a gain in weight.

In Experiment 24 the critical level was not reached and no edema (gain in weight) occurred

The buffer action of the water reserve is evident. The colloids must indeed attract water as the acidity increases, but within a moderate range, this water comes from the "free" portion and becomes fixed. Therefore human beings, as organisms, do not swell or shrink with slight changes in environment. The concentration of the blood as shown by refractometric methods decreased markedly in the first experiment but remained nearly the same in the second.

INTRADERMAL SALT SOLUTION TEST (ALDRICH³)

During the course of these experiments numerous intradermal salt solution tests were made. Physiologic sodium chloride solution, 0.2 cc, was injected and the absorption time noted. By this method also it

TABLE 7—Experiment 21

May 25, 1925	9 00 a m	Male dog, weighing 7.45 kg, received no food or water since 5 p m night before, carbon dioxide combining power of heart blood, 46.3, refractometer reading of plasma, 57
	9 15 a m	Usual food and drink restored
	3 00 p m	50 cc of 2 per cent hydrochloric acid solution by stomach tube
	5 00 p m	All food and water taken away
May 26, 1925	9 15 a m	No food or water since 5 00 p m night before, weight 7.95 kg (gain 0.5 kg), carbon dioxide combining power, 27.3, refractometer reading of plasma, 50

TABLE 8—Experiment 24

May 27, 1925	9 10 a m	Male dog, weighing 9.78 kg, received no food or water since 5 p m night before, carbon dioxide combining power, 53.7, refractometer reading, 56
	9 30 a m	Usual food and water restored
	3 00 p m	70 cc of 2 per cent hydrochloric acid solution by stomach tube
	5 00 p m	All food and water taken away
May 28, 1925	9 00 a m	No food or water since 5 p m night before, weight 9.89 kg, carbon dioxide combining power, 47, refractometer reading, 55

was possible to notice a critical level at which absorption became much more rapid. The difficulties of estimating just when absorption has taken place are considerable and the result would vary with different observers. However, it was clear that real tissue thirst did not begin until the carbon dioxide combining power level fell considerably under 45. Above this level the disappearance time was usually from twenty-five to forty minutes. When the alkali reserve was much below it, from

3 Aldrich, C. A., and McClure, W. B. The Time Required for the Disappearance of Intradermally Injected Salt Solution, *J. A. M. A.* **82**: 293-294 (July 28) 1923, Intradermal Salt Solution Test, Its Prognostic Value in "Nephritis" with Generalized Edema, *J. A. M. A.* **83**: 1425-1428 (May 3) 1924. Aldrich, C. A. The Clinical Course of Generalized Edema, with Suggestions as to Its Possible Function, *J. A. M. A.* **84**: 481-486 (Feb. 14) 1925.

three to ten minutes was the rule. I was unable to set a more accurate critical point or to judge the results in intermediate cases on account of the difficulties of interpretation.

CONCLUSIONS

1 In dogs an amount of water varying from 0 to 72 cc per kilogram of body weight is held in a loose combination with the colloids, perhaps merely acting as a solvent for the colloids and electrolytes.

2 This water reserve in the dog is 0 at the level of 45 of the alkali reserve and rises about 10 cc for each cubic centimeter of the carbon dioxide combining power of plasma.

3 Certain hitherto inexplicable clinical phenomena may be explained on the basis that this water reserve is an active factor in water absorption and excretion.

Further studies are being undertaken to determine the effect of the hydrogen ion concentration on the "free" water, the effect of variations in the water reserve on blood pressure, intra-ocular tension, the use of salt solution dehydration as a measure of the water reserve and the effect of variations in the water reserve on sugar and nitrogen metabolism.

GLUCOSE UTILIZATION IN RENAL GLYCOSURIA

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Renal glycosuria is ordinarily accepted as a condition in which the kidneys are abnormally permeable to glucose. There is usually a constant though not necessarily high excretion of sugar in the urine which is practically uninfluenced by diet. The blood sugar remains at a normal or subnormal level and the symptoms of diabetes mellitus, even in cases that have lasted over a period of years, do not appear. It has also been generally supposed that the body retains its power to utilize and store carbohydrate in a normal manner. The only evidence so far offered that the latter supposition is true is that of Finley and Rabinowitch¹ in a study of the gaseous metabolism of one case.

The present study gives the results of the administration of glucose on the respiratory quotient, total metabolism, blood sugar and glucose excretion in four cases of renal glycosuria. The technic employed in this investigation is that outlined by Boothby and Sandiford,² using a Tissot gasometer and Haldane gas analysis apparatus. Basal periods were first determined after a fast of approximately sixteen hours. Following the basal period blood was obtained for sugar estimation and the glucose then administered. In three of the cases 100 gm. was administered regardless of the weight, in the fourth case, 1.75 gm. per kilogram was given. Twenty minutes after the ingestion of the glucose the mask was adjusted for the first postglucose period. Other periods followed at half-hour intervals so that at least four observations were made following the glucose administration. At the end of each period blood was withdrawn for sugar estimation and urine was obtained for examination if possible.

The respiratory quotients used in apportioning the percentage of calories derived from carbohydrate and fat are not nonprotein quotients. It is realized that the determination of this would perhaps have made the experiments more accurate, yet one cannot be sure that the urinary nitrogen as determined during a short period of observation actually represents the protein destruction of this period. The suggestion of Voit³ and others was adopted of deducting 15 per cent. of the calories

1 Finley, F. G., and Rabinowitch, I. M. Renal Glycosuria, *Quart. J. Med.* **17** 260 (April) 1924. Since the preparation of this paper one other case has been studied by Ladd and Richardson (*J. Biol. Chem.* **63** 681 [April] 1925). This paper, like the others, reports a normal utilization of glucose in renal glycosuria.

2 Boothby, W. M., and Sandiford, I. Laboratory Manual of the Technic of Basal Metabolic Rate Determination, Philadelphia, W. B. Saunders Company, 1920.

3 Voit, E. *Ztschr. f. Biol.* **41** 188, 1901.

as representing the protein metabolized and proportioning the remainder to carbohydrate and fat according to the table of Zuntz and Schumburg as modified by Lusk⁴

REPORT OF CASE

CASE 1—P D, a white man, aged 32, height 173 cm, weight 50 kg, was first observed in 1916. He had had a constant glycosuria uninfluenced by diet for the last nine years. During a period when first observed there was dietary regulation which did not influence the glycosuria. Since that time there had been no dietary regulation, he had remained in excellent health with no symptoms of diabetes mellitus. He was given, under the experimental conditions stated above, 100 gm of glucose. Table 1 shows the results.

TABLE 1—Results in Case 1

	Respiratory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour	Rise Above Normal, per Cent	Calories from Carbohydrate and Fat	Calories from Carbohydrate per Cent	Calories from Carbohydrate	Grams Carbohydrate Utilized	Blood Sugar, Mg per 100 Cc	Urine Sugar, Gm
Basal	0.79	59.9		37.7	-5	51.0	29.9	15.9	3.9	70	0.161
½ hour after 100 gm glucose	0.90	67.1	7.2	42.2	7	57.1	67.5	38.5	9.6	57	0.580
1 hour after	0.92	65.9	6.0	41.4	5	57.0	74.1	42.2	10.5	66	0.500
1½ hours	0.83	61.9	2.0	38.9	-1	52.6	43.8	23.0	5.6	17	0.581
2½ hours	0.89	57.6	-2.3	36.2	-7	48.9	64.2	31.4	7.8	39	0.571
Glucose administered										100.0 gm	
Glucose excreted										2.2 gm	
										97.8 gm	
Glucose metabolized, 16.7 gm, 17 per cent of total											

CASE 2—G W, a white man, aged 39, height 180 cm, weight 59.1 kg, had glycosuria discovered during an insurance examination in 1909. Since that date there had been a more or less constant glycosuria with occasional periods when urinary specimens would be sugar-free. For many months at a time the sugar was constantly present in the urine. There had been no dietary control and no symptoms of diabetes. He had previously had three glucose tolerance tests, all with normal curves except one. The abnormal curve was obtained after the patient had been steadily and heavily using alcohol internally for several days. He was given 100 gm of glucose with the results given in Table 2.

CASE 3—P M, a white man, aged 32, weight 74.6 kg, height 186 cm, had glycosuria discovered during an insurance examination in 1915. No further urinalyses were made until 1923, when during an insurance examination sugar was again detected. The glycosuria disappeared with a marked restriction of carbohydrate. During the last eighteen months he had had many urinalyses, sugar had been found in each specimen examined, but there were no symptoms of diabetes. He was given 100 gm of glucose, Table 3 shows the results.

CASE 4—Mrs F, a white woman, aged 21, weight 47.3 kg, height 157.5 cm, had sugar discovered in the urine during 1922, at this time she was pregnant. Pregnancy was normal and without dietary control, she bore a perfectly healthy child. In July, 1923, she had typhoid fever, hemorrhages and relapse. Every specimen of urine examined since glycosuria was first discovered had shown the presence of sugar. She had never had any symptoms of diabetes. At the time of this observation she was three weeks pregnant, had some nausea and on this account had been on a quite restricted diet. She was given 79 gm of glucose, Table 4 shows the results.

From the accompanying tables it is evident that within one-half hour following the administration of a large dose of glucose there is a noticeable rise in the respiratory quotient, which reaches its highest level from one to one and one-half hours after the ingestion of the glucose. With this rise in the quotient there also is an increase in the basal metabolic rate, from 7 to 19 per cent above normal. A corresponding increase in the calories derived from carbohydrate is evidenced by the tables. The amount of glucose utilized in these cases varied from 14.6 to 18.9 per cent of that ingested, an average of 16.6 per cent for all.

It has previously been shown by Higgins,⁵ Benedict and Carpenter,⁶ Sanger and Hun,⁷ McCann and Hannon⁸ and others, that the normal person, following the ingestion of glucose, responds with a rise in the respiratory quotient within half an hour, although in rare instances there may be a primary fall. However, after one hour the quotient in all cases rises rapidly and approaches 1, which is the respiratory quotient when carbohydrate only is oxidized. There also is an increase in the basal rate from normal to 10 or 20 per cent above normal.

COMMENT

It would seem, therefore, that patients with renal glycosuria metabolize and store carbohydrate in the same way as normal persons. The previous supposition, viz., that patients with renal glycosuria metabolize carbohydrate in a normal way is justified, and so far as the evidence points they do not develop diabetes mellitus.

5 Higgins, H. L. The Rapidity with Which Alcohol and Some Sugars May Serve as Nutrient, *Am J Physiol* **41** 258 (Aug.) 1916.

6 Benedict, F. G., and Carpenter, T. M. Food Ingestion and Energy Transformations, Pub. 261 Carnegie Institute of Washington, pp. 206-208.

7 Sanger, B. J., and Hun, E. G. Glucose Mobilization Rate in Hyperthyroidism, *Arch Int Med* **30** 396 (Sept.) 1922.

8 McCann, W. D., and Hannon, R. R. Studies of Diabetes Mellitus, *Bull Johns Hopkins Hosp* **34** 73 (March) 1923.

THE PHYSIOLOGY OF SYNOVIAL FLUID*

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Little is known concerning the origin and functions of the synovial fluid which has not been the subject of extensive chemical investigation. It is more or less evident that the synovial fluid plays a lubricating rôle in joint structures by virtue of its content of mucin, but to what extent, if at all, it serves as a nutritive medium is not clearly established. In view of the fact that articular cartilage has a small blood supply, the synovial fluid has been regarded as aiding in its growth and nutrition. William Hunter first demonstrated in connection with articular cartilage the existence of the *circulus articulari vasculosus* but this system supplies only the lateral aspects, leaving the bulk of articular cartilage without direct blood supply. Gray¹ refers to articular cartilage as a nonvascular structure.

More than eighty years ago, Toynbee advanced the view that articular cartilage derives its chief pabulum from the plasma exuded by the capillary loops below the subarticular layers of bone. More recently, Strangeways² has again drawn attention to the synovial fluid as a source of nutriment on the basis of the growth observed in fragments of the articular surface which sometimes become loose in the joint.

In a recent series of interesting studies, Fisher³ has reached the opinion that there is an element of truth in each of these views. Using injection methods he has found the subarticular region to be freely permeable and concludes that "it is probable that nutrient plasma is also able to permeate this zone and nourish the deeper layer of the cartilage." Fisher further stresses the recognized anatomic fact that the central articular area of cartilage is removed from contact with either the laterally placed blood vessels or the deeper subarticular tissues and believes that there is a fundamental difference between the structure and nutrition of the central and the lateral regions respectively. In an effort to determine the degree to which the central area may obtain its nutrition through the synovial fluid he has determined the total solids, the protein content and mucin in the supposedly normal synovial fluid of human beings and oxen, and in the lymph plasma of human beings. He found "a somewhat low protein content" but believes, in spite of this fact, that the synovial fluid nourishes the superficial cells of the central articular area. The actual capacity of the synovial fluid to do this was left undetermined.

* From the laboratory of clinical chemistry, Presbyterian Hospital. The work here reported is part of a study on chronic arthritis in collaboration with Dr. Robert B. Osgood of Boston. The expenses were defrayed by contributions from several sources, including a number of patients.

¹ Presented before the Pathological Society, Philadelphia, March 19, 1925.

1 Gray, Henry. *Anatomy*, Ed 22, London, 1923.

2 Strangeways, T. S. P. *Brit. M. J.* 1:661 (May 15) 1920.

3 Fisher, A. G. T. *Lancet* 2:514 (Sept 15) 1923.

Fisher's morphologic studies indicate to him that the synovial membrane differs markedly in its structure at different sites in the same articulation. Near the articular margins, however, there are oval or round connective tissue cells whose function appears to be the secretion of the synovia, including mucin, which he regards as a pure lubricant. The name synovial gland was given to these cells by Havers and it has been suggested that the pressure resulting from the joint movements contributes to expression of their contents into the joint cavity. Fisher also states that the synovial membrane allows the transudation, from the plexus of capillaries, with which it is supplied, of the albuminous fluid that, in his opinion, nourishes the central superficial area of the articular cartilage.

According to Piersol⁴ it is certain that absorption takes place from joints, presumably through the well developed lymphatics found beneath the inner surface of the synovial membrane, but no direct openings into the articular cavity have been demonstrated. Fisher has demonstrated the absorption of potassium iodid, Berlin blue and colloidal silver.

The contact of the internal joint structures with the blood is therefore largely indirect and it is important to ascertain the degree to which the nutritive and other constituents of the blood influence the composition of the synovial fluid. This information is desirable on the physiologic grounds mentioned but also because of its possible bearing on the disease processes affecting cartilage and the associated joint structures in various forms of arthritis. The observations reported here were carried out with the aim of throwing light on some phases of the subject. The problem has been approached, experimentally, in two ways.

1. Certain features of the chemical composition of synovial fluid, as obtained from cases of joint effusion, have been determined and compared with those of blood plasma. Most of the chemical data hitherto available represent work, largely German, carried out before the advent of micro methods, the application of which during the last decade has aided in a quantitative way toward a solution of many physiologic and pathologic problems.

2. In order to study more directly the influence of the blood on the composition of synovial fluid, changes in the concentration of certain constituents of blood have been experimentally produced and the effect of such changes on the composition of joint fluid has been determined.

EXPERIMENTAL WORK

The synovial fluid was obtained by passing a spinal fluid or Wassermann needle into the joint cavity and withdrawing the fluid, under mineral oil, into a syringe. Procain was usually used to anesthetize the site of the puncture. In experiments involving removal of fluid in more than one stage, either a second puncture was made or the needle was allowed to remain in the joint cavity and was held immobile by suitable bandaging.

4 Piersol, G. A. Human Anatomy, Ed. 6, Philadelphia, 1918.

TABLE 1—Composition of Nonpurulent Synovial Fluid

Experiment	Date	Site	pH	Total Carbon Dioxide Content, Percentage by Volume	Sugar, Mg per 100 C c	Lactic Acid, Mg per 100 C c	Non protein Nitrogen, Mg per 100 C c	Uric Acid, Mg per 100 C c	Ash, per Cent	Sodium Chloride, Mg per 100 C c	Calcium, Mg per 100 C c	Viscosity, 20 Degrees	Total Solids, per Cent	Total Nitrogen, per Cent	Total Protein, per Cent
Normal values whole blood															
Normal values plasma															
1	11/ 2/20	Left knee	7.375*	52-61†	77-116†	14-25†	28-39†	3.0-5.0§	0.85	450-500	9-11	17-20†	8.5-9.8†	1.20-1.43†	7.3-8.7†
2	11/ 2/20	Right knee	7.375*	60-71†	77-114†		18-30†			570-620					
3	12/ 8/20	Left knee		57.9	73										
4	12/ 8/20	Left knee		55.2	63									1.16	7.25
5	12/ 8/20	Right knee		68.1	132									0.83	5.19
6	5/24/21	Left knee		62.5	96									1.06	6.63
7	5/24/21	Left knee		67.9	100									0.96	6.00
8	4/25/22	Left knee		68.0	150										
9	3/16/23		7.35	54.2	110		43	4.7					6.34		
10	2/ 8/24		6.99	43.1	69	28		3.4	0.79				7.50		7.25
11	11/11/24	Left knee	7.36	47.0	87		25	4.0	1.10	409			0.13	0.93	5.65
12	12/19/24	Left knee	7.32	54.6	90	13	36		0.96	568	10.7	7.6	7.62		
13	12/11/24	Left knee	7.45	62.0	82			4.3	0.80	513	10.0	16.7			
14	1/11/25	Left knee	7.45	56.8	83		30			415		8.3	7.45	0.80	5.19
15	7/18/25	Left knee	7.47	59.3			41	3.3		633		11.8		0.82	4.87
16	4/11/25	Right knee	7.58	55.2			31	3.5			8.3	3.3	6.25	0.71	4.18
17	4/27/25	Left knee	7.51	49.3	110		24	3.6	0.76	624		3.4	6.44	0.74	4.40
18	5/ 8/25	Left knee	7.42	57.5	105		22	4.4		617		2.7	6.39	0.77	4.68
	6/ 3/25	Left knee								619		2.7	6.03	0.79	4.79

* Van Slyke, D. D. J. Biol. Chem. 18, 153 (Sept.) 1921

† Gram, H. C. Am. J. M. Sc. 168, 511 (Oct.) 1924

‡ Barr, D. P., Himmich, H. J., and Green, R. P. J. Biol. Chem. 55, 495 (March) 1923

§ Lennox, W. G., and O'Connor, M. F. J. Lab. & Clin. Med. 10, 99 (Nov.) 1924

|| Myers, V. O. Practical Chemical Analysis of Blood, 1st ed., C. V. Mosby Company, 1924

¶ Effusion result of trauma fluid bloody, oxygen capacity 6.1 per cent by volume

With one exception, the subjects were patients with arthritis who showed joint effusion. It was difficult or impossible to classify them into morphologic types, such as proliferative and degenerative, but two of the subjects (Subjects P and K) represented intermittent hydrarthrosis, one very typically. The knee was the joint examined in all cases.

The synovial fluid from these cases was light yellow, slightly turbid and nonpurulent. Patient 15 was a normal person with an effusion resulting from trauma and this fluid was highly colored and contained much old blood.

In Table 1 are presented the results of analyses of eighteen synovial fluids. Included in this table, for the sake of comparison, is the range of concentration of each constituent in normal blood and blood plasma.

The following analytic methods were used for blood and synovial fluid. The hydrogen ion concentration was determined by Cullen's colorimetric method⁵ or Hawkin's modification of this method,⁶ the carbon dioxide by the method and apparatus of Van Slyke and Stadie.⁷ Folin's methods were used for the determination of nonprotein nitrogen and glucose.⁸ Uric acid was determined by Benedict's method,⁹ lactic acid by Clausen's,¹⁰ sodium chloride by Whitehorn's method¹¹ and calcium by the method of Kramer and Tisdall.¹² Total nitrogen was determined by a Kjeldahl method and the total protein calculated from the total nitrogen by multiplying by the factor 6.25. When the nonprotein nitrogen had also been determined this was subtracted from the total nitrogen before calculating the protein. Viscosity was measured with a Hess viscosimeter and the results were corrected to 20 degrees. The total solids and ash were determined in the usual way.

With few exceptions, the diffusible constituents, carbon dioxide, sugar, lactic acid, uric acid, nonprotein nitrogen, sodium chloride and calcium were present in synovial fluid in concentrations that are close to the concentrations of the same constituents in normal blood. Fasting arthritic blood has not been shown to diverge from normal in respect to these constituents.

Boots and Cullen¹³ studied the p_H of synovial exudates of patients with rheumatic fever and chronic arthritis and found a p_H range of 7.33

5 Cullen, G. E. *J. Biol. Chem.* **52**: 501 (June) 1922.

6 Hawkins, J. A. *J. Biol. Chem.* **57**: 493 (Sept.) 1923.

7 Van Slyke, D. D., and Stadie, W. C. *J. Biol. Chem.* **49**: 1 (Nov.) 1921.

8 Folin, O. *Laboratory Manual of Biological Chemistry*, Ed. 3, New York, D. Appleton & Co., 1922, pp. 235, 253.

9 Benedict, S. R. *J. Biol. Chem.* **51**: 187 (March) 1922.

10 Clausen, S. W. *J. Biol. Chem.* **53**: 263 (May) 1922.

11 Whitehorn, J. C. *J. Biol. Chem.* **45**: 449 (Feb.) 1921.

12 Kramer, B., and Tisdall, F. F. *J. Biol. Chem.* **46**: 339 (April) 1921.

13 Boots, R. H., and Cullen, G. E. *J. Exper. Med.* **36**: 405 (Oct.) 1922.

to 7.47 in sterile fluid. Fluid from septic joints was more acid, p_H 6.19 and 6.69. In agreement with these authors, the p_H values obtained in the present series, with two exceptions, are within the range of normal blood p_H . There was no evidence of an infected joint in Patient 8, whose joint fluid was p_H 6.99. The carbon dioxide content of this fluid also was low. A rather alkaline reaction, p_H 7.58, was found in the bloody fluid from the patient with knee injury.

The carbon dioxide content of synovial fluid, as revealed by these figures, is in some cases slightly below the range of carbon dioxide content of venous blood plasma. The carbon dioxide figures are not low, however, if the fluid is considered as being in equilibrium with arterial blood.

A few cases of synovial fluid with low sugar content were found, though in general the sugar content is within the range of blood sugar. The fact that the synovial fluid has a content of sugar as high as that of blood is of interest and is an argument in favor of the view that its function is partly nutritional. It is not generally appreciated that cartilage contains considerable amounts of glycogen. Carbohydrate is presumably necessary for replacement and maintenance of glycogen stores, and provision of carbohydrate appears to be relatively more important than provision of nitrogen. Cartilaginous bodies, loose in the joint cavity and growing, find in synovial fluid ample pabulum.

There is no indication, from two observations, that lactic acid is present in synovial fluid in amounts greater than in circulating blood.

The nonprotein nitrogen and uric acid figures give no evidence of accumulation of nitrogenous end products in joints and lend no support to hypotheses that ascribe to uric acid a causative rôle in arthritis.

Since the nonprotein nitrogen content of synovial fluid is comparable to that of blood, it may be inferred that its amino-acid content is likewise similar to that of blood. The amino-acids are the source from which the materials necessary for nitrogenous metabolism may be derived rather than the protein content, as stated by Fisher.

Values for sodium chloride lower than normal plasma values were found in some synovial fluids, though the ash content and calcium content are not far from what have been observed in blood plasma.

The similarity of chemical composition of synovial fluid and blood plasma does not extend to the nondiffusible constituents. As is seen in Table 1, arthritic synovial fluid is low in total solids and total protein when compared with blood plasma. As already mentioned, Fisher has also found a low protein content in synovial fluids obtained postmortem from normal (?) joints. Despite its low protein content, the viscosity of synovial fluid is high, in some cases from four to five times greater

than that of plasma Salkowski¹⁴ and later Von Holst¹⁵ isolated from synovial fluid mucin-like proteins, serosamucins as Von Holst termed them

In view of the low protein content of synovial fluid, the "sticky" nature and high viscosity suggest that its particular characteristics, distinctive from blood and plasma, are due to the contained mucin

Experiments were carried out in which the blood and synovial fluid were analyzed before and after giving 100 gm of glucose by mouth The results of four such experiments, which are given in Table 2, reveal a communion of the synovial fluid with the alimentary tract that is novel

TABLE 2—*Effect of Ingestion of Glucose on the Composition of Synovial Fluid and of Venous Blood*

Sample	Time, A M	Sugar, Mg per 100 C c	Viscosity, 20 Degrees	Total Solids, per Cent	Uric Acid, Mg per 100 C c	Sodium Chloride, Mg per 100 C c	Total Nitrogen, per Cent
Experiment 1, Subject K, Nov 21, 1924							
Blood 1	10 10	86			4 3	409	
Synovial fluid 1	10 15	82	11 8	7 62	4 3	513	
100 gm glucose by mouth	10 20						
Blood 2	10 55	167			4 5	367	
Synovial fluid 2	11 05	171	8 1	7 20	4 4	546	
Blood 3	11 25	153			4 6	399	
Synovial fluid 3	11 35	171	4 9	6 16	1 4	566	
Experiment 2, Subject K, May 18, 1925							
Blood 1	11 50	95					
100 gm glucose by mouth	11 58						
Blood 2	12 40	142					
Synovial fluid 1	12 35	160	11 8				
Blood 3	1 25	128					
Synovial fluid 2	1 20	163	9 6				
Experiment 3, Subject C, May 8, 1925							
100 gm glucose by mouth	9 15						
Blood 1	10 05	116			4 4		
Synovial fluid 1	10 05	135	2 7	6 39	4 4	617	
Blood 2	11 05	80			4 1	493	
Experiment 4, Subject P, Dec 19, 1924							
Blood 1	9 35	99					
Synovial fluid 1	10 15	90	7 6	6 13			0 93
100 gm glucose by mouth*	10 20-30						
Blood 2	11 20	125					
Synovial fluid 2	11 05	101	7 0	6 15			0 85

* Subject nauseated, only three fourths of sugar dose consumed

and not heretofore suspected The rise in blood sugar following glucose ingestion promptly causes a rise in sugar concentration within the joint with no evidence of a lag In Experiments 2 and 3 the concentration of sugar in the synovial fluid, half an hour and one hour after the taking of the sugar, was higher than the concentration of sugar in the blood at these times This may mean that there is a tendency for sugar to accumulate in the joint cavity, though it seems more likely that it represents an equilibrium with respect to sugar between arterial blood and synovial

14 Salkowski, E Virchows Arch f path Anat **131** 304, 1893

15 Von Holst, G Ztschr f physiol Chem **43** 145, 1904-1905

fluid The analyses were made on venous blood, which usually has a much lower sugar content, following sugar ingestion, than has arterial blood Experiment 4 was the least successful of those conducted The subject was extremely nauseated as a result of the joint puncture and dose of sugar, being unable to consume all of the sugar solution In this case, fifteen minutes elapsed between the second venous puncture and the second joint puncture, a lapse of time during which the level of circulating sugar may have materially changed

It will be seen that the viscosity of the synovial fluid became progressively lower as samples were removed from the joint A fall in viscosity has usually been observed when the joint is tapped in successive stages with a suitable time interval between punctures This indicates a dilution of the fluid remaining in the joint cavity with a more watery liquid

TABLE 3—*Effect of Ingestion of Sodium Bicarbonate on the Composition of Synovial Fluid and Blood*

Sample	Time, P M	Total Carbon Dioxid, Capacity, per Volume	Carbon Dioxid, per Volume	<i>pu</i>	Viscos- ity, 20 Degrees	Solids, per Cent
Experiment 1, Subject K, Jan 11, 1925						
Blood 1*	12 50	50.7		7.45		
Synovial fluid 1	12 55	50.4		7.45	7.5	7.36
10 gm sodium bicarbonate by mouth	1 03					
Blood 2	1 39	59.6		7.33		
Synovial fluid 2	1 45	61.0		7.45	7.1	7.08
Experiment 2, Subject K, May 18, 1925						
Blood 1†	12 40	55.4	63.8	7.42		
Synovial fluid 1	12 35	59.3		7.47	11.8	
10 gm sodium bicarbonate by mouth	12 45					
Blood 2	1 23	62.2	64.7	7.40		
Synovial fluid 2	1 20	59.9		7.47	9.6	

* Four minutes after electric "bake"

† Forty two minutes after sugar ingestion

The entry of sugar into the joint is not, however, to be ascribed merely to refilling of the partly emptied cavity with a sugar-rich fluid from the blood In Experiments 2 and 3, the initial tapping of the joint was purposely delayed until after the sugar had been administered The fasting level of synovial fluid sugar in the subjects of these experiments had previously been determined A prompt rise of sugar in the synovial fluid was observed under these conditions, precisely as had been observed when the joint cavity was partly emptied and refilling was taking place

The ease with which glucose can gain access to the joint cavity gives definite basis to the view that regards synovial fluid as a pabulum from which the tissues bathed by it, especially the central area of the articular cartilage, may derive their nutrient requirements This fact obviously suggests that other diffusible substances may behave likewise

The possibility of entry of harmful as well as nutritive substances is further suggested and emphasizes the necessity of regarding the gastrointestinal tract as a source of possibly undue amounts of normal products of digestion as well as toxic material

Two experiments were carried out in which a solution containing 10 gm of sodium bicarbonate was given each of two subjects and the effect on the blood and synovial fluid observed Collip and Bakus¹⁶ report a lag in changes in alkali reserve in spinal fluid when such changes are induced in the blood by bicarbonate feeding The results of the present experiments are given in Table 3 In both cases a rise in carbon dioxide content of blood followed the ingestion of bicarbonate In Experiment 1 the carbon dioxide content of the blood rose 8.9 per cent by volume and in the same time the carbon dioxide content of the synovial fluid rose 4.6 per cent by volume In the second experiment no increase in carbon dioxide content of the synovial fluid was observed, though the blood carbon dioxide increased 7 per cent by volume There was no increase in the carbon dioxide capacity of this blood, however, in spite of the bicarbonate feeding

It has previously been shown by us¹⁷ that the blood of a subject exposed to external heat in an electric cabinet during a forty minute "bake" may become more alkaline as a result of loss of carbon dioxide In order to determine whether the contact of the synovial fluid with the blood is sufficiently intimate to induce similar changes in the synovial fluid, the p_{H} and carbon dioxide content of the blood and the synovial fluid of patients with joint effusion were determined before and after exposure to external heat This consisted, as in the previous studies, in a thirty to forty minute "bake" in an electric baker

Five experiments of this kind were carried out and the results are given in Table 4 An alkaline swing in the blood, of sufficient magnitude to be significant, was induced in only two of the experiments (Experiments 1 and 4) In these two cases there was no change in the p_{H} of the synovial fluid or in its carbon dioxide content despite the changes that occurred in the blood It is difficult to interpret these results The conclusion that gas exchange between blood and synovial fluid does not take place freely is perhaps not justified Such a conclusion would not harmonize well with the clear cut experiments showing the passage of glucose from blood to synovial fluid Little is known of the base binding capacity of the proteins peculiar to synovial fluid and the ability of such a buffered fluid to resist changes in reaction Further, in these experiments, the p_{H} was determined in all cases by Cullen's colorimetric method,

16 Collip, J. B., and Bakus, P. L. *Am. J. Physiol.* **51**: 551 (April) 1920

17 Cajori, F. A., Crouter, C. Y., and Pemberton, R. *J. Biol. Chem.* **57**: 217 (Aug.) 1923

which involves a large empirical correction. It has recently been shown¹⁸ that this correction is not a constant and may vary widely in blood in which the protein content is altered as after hemorrhage. It may be that in the experiments here reported, p_H changes are masked, when determined colorimetrically. Further work will be carried out in an endeavor to clarify this phase of the subject.

TABLE 4—*Effect of Exposure to External Heat on Composition of Synovial Fluid and Venous Blood*

Sample	Time, A. M.	Body Temperature, F.	p_H	Total Carbon Dioxide, per Cent by Volume	Viscos- ity, 20 Degrees	Solids, per Cent	Uric Acid, Mg. per 100 Cc.
Experiment 1, Subject D, Feb. 8, 1924							
Blood 1	10 00		7.30				
Synovial fluid 1	10 25		6.99	43.1		6.34	3.4
Electric "bake" began	10 40	98.6					
ended	11 25	100.0					
Blood 2	11 30		7.43	51.1			
Synovial fluid 2	11 30		6.96	44.5		6.76	3.3
Experiment 2, Subject M, Nov. 14, 1924							
Blood 1	9 30		7.41	49.4			3.8
Synovial fluid 1	10 10		7.36	47.0		7.50	4.0
Electric "bake" began	10 20						
ended	10 50	99.2					
Blood 2	11 00		7.44	49.9			3.8
Synovial fluid 2*	11 25		7.36	48.4		7.49	4.3
Experiment 3, Subject K, Dec. 11, 1924							
Blood 1	11 14		7.41	54.0			
Synovial fluid 1	11 30		7.43	56.8	16.7		
Electric "bake" began	11 42						
ended	12 15	99.4					
Blood 2	12 25		7.43	53.2			
Synovial fluid 2	12 35		7.43	55.0	12.3		
Experiment 4, Subject K, Jan. 11, 1925							
Blood 1	12 00		7.37	53.6			
Synovial fluid 1	11 50		7.45	56.4	8.3	7.45	
Electric "bake" began	12 06	98.2					
ended	12 44	99.6					
Blood 2	12 50		7.45	50.7			
Synovial fluid 2	12 55		7.46	56.4	7.5	7.36	
Experiment 5, Subject C, June 3, 1925							
Blood 1	9 45		7.42	53.3			
Synovial fluid 1	10 15		7.42	57.5	2.7	6.03	
Electric "bake" began	10 30	98.3					
ended	11 05	99.4					
Blood 2	11 07		7.42	54.8			
Synovial fluid 2	11 07		7.46	57.6	3.1	6.35	

* Fluid removed with difficulty and much pain.

SUMMARY

The concentration of certain of the chemical constituents of non-purulent synovial fluid from arthritic patients with joint effusion has been determined.

Changes in the composition of the blood have been induced experimentally by glucose feeding, administration of sodium bicarbonate and

exposure to external heat. The effect of such blood changes on the composition of synovial fluid has been observed.

The concentration of the diffusible constituents of synovial fluid, uninfluenced by experimental feeding, closely approaches that of blood plasma. It has been found that, following glucose ingestion, the sugar concentration of synovial fluid promptly rises to a level as high as, or higher than, that in venous blood.

It is concluded from such experiments that diffusible substances pass easily from the blood to the synovial fluid and that the gastrointestinal tract must be regarded as being in surprisingly close communion with the joint fluids. The possibility of detriment from this source is pointed out.

The adequacy of the synovial fluid for the nutrition of cartilage from the standpoint of carbohydrate and energy yielding content is clearly indicated.

Experiments involving changes in the acid-base equilibrium of the blood have not shown corresponding changes in the synovial fluid. Further work will be necessary before these results can be satisfactorily explained.

BLOOD SUGAR CURVES IN EPIDEMIC ENCEPHALITIS *

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The increase in the sugar content of the spinal fluid in epidemic encephalitis led us to investigate the sugar metabolism of patients suffering from this disease by means of the blood sugar curve. This method of studying the sugar metabolism has been criticized by a number of observers. Fitz's ¹ careful studies have shown that all the ingested glucose may not be absorbed, and Rowe ² has abandoned the glucose curve in his studies of endocrinopathies. However, Gray ³ from an analysis of 4,000 curves was able to define the limits of variation of the blood sugar after the ingestion of glucose with sufficient accuracy to indicate that information about the sugar metabolism may be obtained by this method.

Alexander ⁴ states that the sugar curve in encephalitis tends to be higher than normal and, in the single curve plotted, the sugar goes up to 240 mg per hundred cubic centimeters at the end of the first hour. Thalheimer and Updegraff ⁵ believe that there is a quantitative relationship between the sugar content of the blood and the spinal fluid in epidemic encephalitis. They emphasize the fact that all their blood sugar values were high and that some were definitely above normal. In the twenty-eight cases reported by them, the blood sugar varied between 115 and 297 mg per hundred cubic centimeters, while the spinal fluid sugar varied between 54 and 234 mg per hundred cubic centimeters. They also remark that the sugar of the spinal fluid shows an increase only when the blood sugar is above a certain level. These observers believe that there is a threshold level for the entrance of sugar into the spinal fluid similar to that maintained by the kidneys for sugar in the urine. Kraus and Pardee ⁶ in twelve cases of epidemic encephalitis

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1 Bryan, A. W., Cathcart, E. P., Fitz, R., and Buler, C. An Improved Alimentary Glucose Tolerance Test, *J. Metabolic Res.* **1** 549 (April) 1922.

2 Rowe, A. W. Metabolism of Galactose, Threshold of Tolerance in Normal Adults, *Arch. Int. Med.* **34** 388 (Sept.) 1924.

3 Gray, H. Blood Sugar Standards, *Arch. Int. Med.* **31** 241 (Feb.) 1923.

4 Alexander, M. E. Epidemic Encephalitis, *Arch. Neurol. & Psychiat.* **6** 44 (July) 1921.

5 Thalheimer, W., and Updegraff, H. Epidemic Encephalitis, *Arch. Neurol. & Psychiat.* **8** 15 (July) 1922.

6 Kraus, W. M., and Pardee, I. H. The Serology of the Spinal Fluid and Blood in Epidemic Encephalitis, *Arch. Neurol. & Psychiat.* **5** 710 (June) 1921.

near the acute stage report the fasting blood sugar varying from 75 to 170 mg per hundred cubic centimeters Wilcox and Lyttle,⁷ in eleven cases of epidemic encephalitis, found the fasting blood sugar to be from 81 to 143 mg per hundred cubic centimeters and the spinal fluid sugar to vary from 51 to 121 mg per hundred cubic centimeters

Our cases have been studied by the "blood sugar tolerance test" of Janney and Isaacson,⁸ in which the dose of glucose is based on the patient's weight (175 gm per kilogram) and samples of blood are withdrawn one, two and three hours after the ingestion of glucose Sugar determinations were made by the method of Folin and Wu⁹ Our results are shown in the accompanying table, all the significant laboratory data are included here The Wassermann reaction was negative in every case None of the patients had glycosuria The accompanying reports of the cases give only positive clinical findings Of the seventeen cases here reported only four of the patients were seen in the acute febrile stage, though in no case was the clinical diagnosis in doubt It must be remembered that we are here dealing only with the mental sequelae of epidemic encephalitis and the possibility of these findings not being characteristic of the disease as a whole must be borne in mind

In considering the results of these experiments one is struck by the number of "flat" and "high" curves Gray's figures at the end of the first hour after the ingestion of glucose show that 50 per cent of the figures lie between 110 and 160 mg per hundred cubic centimeters, whereas only four of the twenty-four curves in these cases lie within these limits In Gray's series only 13 per cent of the figures were over 140 mg while in this group 40 per cent fall above this figure This contrast is so striking that despite the small numbers it is statistically valid in demonstrating a deviation from Gray's normal group If this group of patients is divided according to age there are eight children and nine adults It seems significant that the preponderance of values above 160 mg should occur in the latter group whereas the children tend to show the flat curve—possibly a reversion to the infantile type of curve coincident with the mental reversion observed in these cases

Case 11 showed an interesting change toward the "normal" as the disease progressed from the acute stage Case 17 also showed some change, which was coincident with clinical changes Case 9 showed distinct clinical improvement at the time of the second curve which is nearer the norm than the first

7 Wilcox, H B, and Lyttle, J D The Diagnostic Value of Sugar Concentration in Spinal Fluid, *Arch Pediat* **40** 215, 1923

8 Foster, H E Hyperglycorachia in Encephalitis, *J A M A* **76** 1300 (May 7) 1921

9 Folin, O A Laboratory Manual of Biological Chemistry, New York, D Appleton & Co, 1922

Data in Seventeen Cases

Case	Sex*	Age	Weight in Pounds (kilograms)	Date of Curve	Blood Sugar Curve, Mg per 100 C c				Spinul Fluid					Remarks	
					Fast ing	First Hour	Second Hour	Thrd Hour	Albu min	Glob ulin	Cells	Mg per 100 C c			Colloidal Gold Reaction
1	♀	9	54 (24.5)	2/14/25	74	100	111	—	—	0	5	18	50	Nega- tive	Glucose given by nasal tube Temperature 101.5 (rectal) Basal metabolic rate, —1% Basal metabolic rate, —2% Basal metabolic rate, +16% after thyroid extract for ten days
2	♂	9	67 (30.4)	4/29/25	71	94	96	104	—	—	—	—	—	—	
3	♂	10	114 (51.7)	2/20/25	87	100	127	132	—	0	0	15	65	Nega tive	
4	♂	10	53 (26.3)	4/29/25	95	118	101	99	—	—	—	—	—	—	
5	♂	11	100 (45.4)	2/ 6/25	91	83	99	83	—	—	—	—	—	—	
6	♂	12	64 (29)	4/29/25	86	143	111	63	—	—	—	—	—	—	
7	♀	13	103 (46.7)	2/21/25	133	168	150	150	++	0	66	—	88	Nega tive	
8	♂	13	96 (43.5)	9/ 6/24	105	95	81	103	—	—	—	—	—	—	
9	♀	18	94 (42.6)	9/ 6/24	105	250	222	146	—	0	1	44	80	Nega tive	
10	♂	24	127 (57.6)	2/25/25	76	92	133	112	—	0	3	82	69	Nega tive	
11	♂	24	143 (64.9)	1/30/25	89	87	92	89	—	—	—	—	75	Nega- tive	
				2/18/25	88	200	127	85	—	—	—	—	—	—	
				2/ 9/25	100	250	185	138	—	0	5	22	—	—	
				2/15/25	98	102	111	97	—	—	—	—	—	—	
				3/12/25	81	98	106	80	—	—	—	—	—	—	
				3/27/25	87	118	118	105	—	—	—	—	—	—	
12	♂	25	131 (59.4)	3/26/25	94	92	108	84	—	—	4	45	91	Nega tive	
13	♂	31	110 (49.9)	1/21/25	133	103	87	80	—	1	22	74	64	Nega- tive	
14	♂	31	152 (68.9)	3/27/25	84	116	113	100	—	—	—	—	—	—	
15	♀	32	143 (64.9)	2/11/25	120	216	148	91	—	0	3	69	82	Nega tive	
16	♀	34	208 (94.3)	1/15/24	105	—	138	116	++	0	1	—	79	Nega- tive	
17	♂	34	161 (73)	3/31/24	105	238	227	207	—	—	—	—	—	—	
				5/26/24	89	339	192	97	—	—	—	—	—	—	
				2/22/25	115	189	129	—	—	—	—	—	—	—	

* In this column, ♂ indicates male ♀ female

It seems evident from the foregoing that a disturbance in the sugar metabolism is associated with the underlying pathology of this disease. The blood sugar tolerance curve apparently is a more sensitive indicator of this disturbance than the spinal fluid sugar with which it is probably intimately connected. It is noteworthy that the fasting blood sugar values in this group are not high and that the same is true of the spinal fluid "sugars" though the latter are with two exceptions in the higher half of the normal range.

SUMMARY

1 Twenty-four blood sugar curves according to the technic of Janney and Isaacson were performed in seventeen cases diagnosed epidemic encephalitis or its sequelae.

2 The blood sugar curve in epidemic encephalitis and the post-encephalitic state was found to deviate from the best established norm with such frequency that we may conclude that there is a fundamental disturbance of the sugar metabolism in this disease.

3 The derangement of the sugar metabolism persists in patients suffering from mental sequelae of this disease.

REPORT OF CASES

CASE 1—A girl, aged 9 years, was admitted, Feb 11, 1925, with the complaint of boisterousness and running away from home. Five years before the patient had a febrile attack during which she slept for three days and three nights. Following this she was sleepy for six weeks. Since that time there had been twitching of the hands and feet and a complete personality change in that she became disobedient, disorderly, antagonistic, restless and ran away from home. The pupils were unequal, and the tonsils were prominent. On account of extreme overactivity and aggressiveness, the patient was committed to the Foxboro State Hospital February 28 unimproved.

CASE 2—A boy, aged 9 years, was admitted, April 28, 1925, with the history that in October, 1924, he had had a febrile attack on account of which he had to stay in bed for several weeks. During this attack he saw "two mothers" (evidently diplopia). Following the attack the patient became very sleepy during the day and used to fall asleep with his feet in the oven. Gradually personality changes became noticeable, he became aggressive, irritable, poor in school, hyperactive during the night and sleepy during the day. He began to drool copiously and attack the other children. He is still in the hospital.

CASE 3—A boy, aged 10 years, was admitted, Feb 19, 1925, with the complaint of drowsiness. Five months before the patient was ill and the family physician told the parents that the patient had chorea. There was no fever but there was constant twitching of the muscles of the face. He was ill for six days but felt poorly for two weeks. February 14, he began to complain of headache and immediately went to bed, where he had remained in a stuporous condition. His nose twitched and he slept most of the time. He only took a little liquid nourishment, had no fever, vomited several times. He was delirious for one day and had been incontinent. He had gradually improved. Since the attack of "chorea" in September, 1924, he is quite a different boy, irritable and with completely changed tastes, mode of life, sympathies and affections. He had to be away from school most of the term because he became nervous and forgetful. Examination showed nothing except generalized tremors. There had been gradual ethical deterioration—stealing, lying and a complete personality change.

CASE 4—A boy, aged 10 years, was admitted, April 21, 1925, with the history that he had epidemic encephalitis in December, 1924, and was at the City Hospital during January and February, 1925. Following his discharge from the hospital he began to have frequent attacks at night in which he closed his fists until the nails cut the skin of the palm of the hand. Physical examination showed a sleepy, immobile expression of the face, a drooping posture and fine tremors of the extended fingers. During his stay in the hospital there was noted reversal of the sleep rhythm, lethargy, periods of restless agitation with an agonized expression of the face, occasional muscular tension, and short intervals of hyperpnea lasting only two or three respirations. The intellectual functions seem to be well preserved and there is no evidence of deviation of conduct. The patient is still in the hospital.

CASE 5—A boy, aged 11 years, was admitted, Feb. 11, 1925, with the complaint of stealing. In 1919 the patient had whooping cough followed by the extreme desire to sleep most of the day. There was a history of diplopia at this time. Examination showed a fixed expression of the face and drowsiness. He is still in the hospital.

CASE 6—A boy, aged 12 years, was admitted, April 21, 1925, with the history that in December, 1924, the family had noticed that he became very sleepy, refused to get up in the morning and slept until noon. At night he was not sleepy at all. In January the patient had a severe cold and was admitted to the children's clinic of the Massachusetts General Hospital where a diagnosis of epidemic encephalitis was made. Following discharge from the Massachusetts General Hospital in March, 1925, he was sleepy most of the time. At night he was talkative, irritable, at times violent and once attacked his father with a knife. In April, 1925, the patient was at the Long Island Hospital but he had to be discharged because he was attacking nurses and patients.

On physical examination a slight drooping posture was noticed, retardation of all movements and a sleepy, immobile facial expression. In the ward the patient showed marked untidiness, constant blowing of the nose, complete reversal of the sleep cycle and constant spitting. The mental examination was negative with the exception of ethical deterioration. The patient is still in the hospital.

CASE 7—A girl, aged 13 years, was admitted, Feb. 12, 1925, with the history that she was admitted to the Boston City Hospital, Nov. 19, 1924, and that her condition had there been diagnosed epidemic encephalitis. The spinal fluid at this time showed 70 cells and 0.061 per cent sugar. She was discharged, Dec. 30, 1924, unimproved. During her convalescence it was noticed that she became confused, dull and restless, and was not able to focus her attention. On admission she was drowsy and dozing most of the time. Occasionally she cried for a few minutes, then began to doze again. Physical examination showed a frail looking semistuporous girl. Abdominal reflexes were absent. There was some difference in the plantar reflexes, extension on the right being followed by flexion. After two weeks in the hospital the patient was still extremely drowsy and lethargic.

CASE 8—A boy, aged 13 years, was admitted, June 30, 1924, with a complaint of fainting and yawning spells. In March, 1923, he had a febrile attack of a few days' duration which was thought to be a cold. Following the attack he became sleepy in school, poor in his studies and extremely restless at night, keeping the whole house awake by continuous activity. He made and remade his bed twelve times during the night. In April, 1924, he developed spitting and yawning habits as well as fainting attacks.

On admission the patient was extremely restless, constantly getting out of bed, throwing his head backward in a yawning-like motion and expectorating all around him. At night he was sleepless and overactive. The intellectual functions were intact. There was extreme scattering of the attention and lack of continuity of effort. During his stay at the hospital there was gradual deterioration, with almost continuous yawning spells, and he spit all over the ward, which made him a difficult problem. In January, 1925, he was transferred to the Danvers State Hospital, unimproved.

CASE 9—A woman, aged 18, was admitted to the hospital, Sept 4, 1924, with the complaint that she would not talk, that she sat in her room and fainted frequently. In June, 1924, the patient had a febrile attack that was thought to be tonsillitis. In the attack the patient complained of difficulty of vision. Following the attack she became very quiet and seemed to like to be alone. She refused to eat and slept very little. On admission the patient was stuporous and incontinent.

On physical examination, the pupils were unequal and reacted sluggishly to light through a very narrow arc. The tendon reflexes could only be obtained on reinforcement. The left knee jerk was easier to elicit than the right. The thyroid was slightly enlarged. The mental condition was that of a stupor. At times she obeyed very simple commands, but she was uncooperative and resistive during physical examination.

On the fifth day after admission, the patient seemed brighter and complained of having lost her memory. She asked one of her sisters when her head would be cut. After about three weeks in the hospital she became a little brighter, took more interest in her surroundings, and would answer simple questions by a nod of the head. The course varied for about two months between slight improvement and regression to a stuporous condition until December, 1924, since then she has shown improvement and is still in the hospital.

CASE 10—A man, aged 24, was admitted, Jan 16, 1925, with a complaint of confusion and stupor. There was no history of any acute infection. In September, 1924, the patient complained of being tired, he stressed the necessity of rest, and became somewhat seclusive and inefficient in his work. The family noticed that he became gradually more and more drowsy, occasionally accusing himself of inability to work. Physical examination showed an undernourished sick boy with swollen, bleeding lips and a red face. The temperature was 101. He had to be tube fed. He was very confused. There was gradual deterioration. The patient is now in the hospital, the condition essentially the same.

CASE 11—A man, aged 24, was admitted, Jan 13, 1925, with the complaint of drowsiness and sleepiness. In 1919, the patient had epidemic encephalitis and was sick for eight or ten months. He became irritable, restless and had constant headaches, since 1922 he had been under the care of the Veterans' Bureau. Examination showed a fairly well developed young man with generalized tremors, especially of the tongue and fingers, active reflexes, unequal pupils, slight swaying in Romberg's position and a stooping posture. He was restless, had frequent shiver-like tremors, and vague hallucinations, with a good preservation of intellectual functions. He fell asleep frequently and had to be awakened for his meals.

CASE 12—A man, aged 25, was admitted, March 3, 1925, with the history that, on January 13, he had suddenly felt weak and had passed urine very frequently. February 21, he became very weak and excited. At this time sudorrrhea was noted. He had to go to bed and in the morning complained of dizziness and severe headache. On the following morning he had a convulsion, tonic in type. He stayed in bed for four days and on the fifth day became unconscious. That night he threw himself on the floor and made a few jerky movements with hands clenched, this attack lasted for about five minutes. March 3, he had two spells in which he became rigid and stiff. He did not bite his tongue and was not incontinent. There was no history of vomiting nor diplopia. Physical examination was negative. The temperature was 103 F.

On admission, the patient appeared dazed and toxic, and remained motionless with eyes staring straight ahead. He answered only in monosyllables and by a nod of his head admitted visual hallucinations. On the third day after admission, the temperature dropped to normal and he became more alert, although he still had extreme difficulty in carrying out simple commands and in understanding and comprehending simple questions. There was a purposeless shifting in the direction of the eyes and head. He is still in the hospital.

CASE 13—A man, aged 31, was admitted, Jan 6, 1925, with a complaint of failing vision, confusion and restlessness. Dec 20, 1924, the patient complained that "his eyes were blurry" and said that he saw double. December 21, an optician told him that he had a "twisted optic nerve." Since that time the patient had been extremely fidgety and the family noticed that since January 1 he had slept excessively. At night he jumped and twitched in his sleep. He was delirious and while at home he imagined that he was at work. He was a poorly developed and poorly nourished adult with small, irregular and unequal pupils which did not react to light or accommodation. He had vertical nystagmus and slight right external strabismus in the primary position. The eye movements were jerkily performed, and there were jelly-like nystagmoid movements on lateral fixation. There was poor convergence, especially on the right. Both external recti were weak, more so on the right, the left rectus was weak except on conjoined movement. Upward and downward movements were poorly done, and there was bilateral partial ptosis, the left greater than the right. There were poorly coordinated eye movements. The mental examination showed underactivity, slight stupor, vague delusions and hallucinations, and initial retardation of speech. The patient was discharged, Jan 27, 1925, unimproved and in a state of slight confusion.

CASE 14—A man, aged 31, was admitted, March 23, 1925, with the history that six years before he was in bed for a week during which period he perspired freely and was weak and had diplopia. About three years before he noticed trembling of his legs and later trembling of his arms and backache, which had persisted to the present time. For the last few years the patient showed some personality change, abnormal sex appetite, affective swings and irritability.

Physical examination showed a masklike expression of the face and slowing of the gait, with loss of associated movements, resembling the parkinsonian syndrome. There was a fine, constant involuntary tremor of the head, hands and legs. The pupils reacted poorly to light, better to accommodation. The tendon reflexes were decreased. During the patient's residence in the hospital a normal underactivity was observed, with a great deal of sleeping in the ward during the day, slight depression, vague delusions and general impairment of the intellectual functions in the field of reasoning and judgment. The patient was discharged after ten days, his condition unchanged.

CASE 15—A woman, aged 32, was admitted, Feb 7, 1925, with the complaint that she had ideas about the necessity of impregnation by a young man. Five years before she had an attack of influenza. Following this her husband noticed that she became very sleepy and fatigued easily. The family noticed that "her face had dropped." Her judgment became impaired. She became somewhat euphoric and entered into all kinds of business ventures without success.

On admission there was definite masklike expression of the face, generalized tremors, stooping, rigid gait and unequal pupils. Mentally she was clear, but she was slightly euphoric and had vague hallucinatory experiences. March 13, the patient was discharged to the Westboro State Hospital, unimproved.

CASE 16—A woman, aged 34, was admitted, Jan 10, 1924, with a complaint of weakness, tremors and visual hallucinations. Five years before she had two attacks of influenza which lasted over ten weeks, during which she was drowsy and saw double. Since that time, her friends noticed that she did not do her housework as well, and that she developed tremors and peculiar facial expressions. She had definite epidemic encephalitis with stupor four years before. On admission she showed a masklike expression, obesity, loss of associated movements in walking, a forward stooping posture, slow hesitating speech, transient tremors, sluggish pupils, hyperactive reflexes, and clog-wheel resistance to flexion. The whole picture was very suggestive of Parkinson's syndrome. January 13, the patient was committed to the Boston State Hospital, unimproved.

CASE 17—A man, aged 34, was admitted, March 17, 1924, with the complaint that he did not answer questions. For three months before admission the patient became very quiet, silent and uncommunicative. On admission he was in a stupor. There was no fever. There was loss of associated movements in

walking, a masklike expression of the face, and an extremely profuse sebaceous secretion over the face, producing the typical "ointment face." There was extreme retardation in initiating the simplest movements, although the patient apparently had no difficulty in understanding commands. The mental status was that of a stupor with complete mutism. Tears welled up into his eyes when he made an effort to answer questions, and he paid no attention to his surroundings. He remained in bed for three months. After six months he began to talk in a low whisper, and there has been gradual improvement in that the patient has begun to move around and help with simple routine work. Gradually the parkinsonian facies has disappeared, but the mental state is still one of confusion and he is still in the hospital.

INTESTINAL CHEMISTRY

III SALIVARY DIGESTION IN THE HUMAN STOMACH AND INTESTINES *

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In estimating the importance of salivary digestion in man studies must be made on the human subject. The salivas of the dog and cat have little or no action on starch whereas human saliva is powerfully amylolytic. Salivary digestion in man is influenced by psychic factors and by conditions of mastication and of gastric motility which cannot be exactly simulated in lower animals.

Numerous experiments have been carried out on the digestion of starch by human saliva but very few attempts have been made actually to follow the course of this digestion as it occurs in the human stomach. Most of these few experiments have been merely qualitative or otherwise inadequate. The best work appears to be that of Muller,¹ who obtained the gastric contents following a test meal by expression and determined the percentage of soluble carbohydrate.

The present series of experiments were carried out using the retention stomach tube, which does not appear to have been previously used for this purpose. The subjects were dental students of apparently normal digestive function. They reported at 1 p. m. The stomach tubes were passed and residuums examined for free hydrochloric acid. In one case this was not present and the complete residuum was removed to exclude the possible influence of pancreatic amylase. Subjects were cautioned not to swallow saliva until food was given. The test meals consisted of 100 gm portions of boiled and mashed potatoes or 75 gm of bread without crust. Ferric hydrate equivalent to 0.15 per cent of iron was mixed with the potatoes and an amount equivalent to 0.088 per cent of iron was incorporated in the bread flour. The iron was used as a control on sampling, and being practically insoluble should have no effect on the course of digestion.

Subjects were requested to masticate in a reasonably thorough manner. The time required was noted. Fifteen minutes after the last food was swallowed (about half an hour after the first of the food was taken) and at fifteen minute intervals thereafter gastric specimens were

* From the Laboratory of Physiological Chemistry, University of Illinois College of Medicine

1 Muller, J. Ueber den Umfang des Starkeverdaunung im Mund und Magen des Menschen, Verhandl. d. Cong. f. inn. Med. **19** 321, 1901

removed for examination. The experiment was discontinued after forty-five minutes as by this time salivary digestion had been stopped by the gastric acid.

Seven cubic centimeters of gastric contents were removed each time. One cubic centimeter was titrated for free hydrochloric acid, using Topfer's reagent as the indicator. One cubic centimeter was tested for active amylase by adding 5 c.c. of 1 per cent soluble starch and testing for undecomposed starch after two hours and after eighteen hours. The other 5 c.c. was used to determine the degree of digestion of the starch. For this purpose the specimen withdrawn with a graduated syringe was introduced at once into a test tube containing 15 c.c. of 0.5 per cent hydrochloric acid and the whole mixed, thus stopping starch digestion. The mixture was made faintly alkaline to phenolphthalein and heated to boiling for several minutes to get as much as possible of the starch into solution, then cooled and made just acid with acid sodium phosphate solution. The mixture was shaken to obtain a uniform suspension and while still being shaken 5 c.c. portions were pipetted out by means of a pipet with a tip of rather large bore into a series of three test tubes. One portion was filtered at once and the reducing carbohydrate was determined. 1 c.c. of the filtrate was treated with 3 c.c. of 0.2 per cent picric acid and 0.5 c.c. of 5 per cent sodium hydroxide and heated on the boiling water bath for ten minutes, this was then diluted with 20 c.c. of water and compared in a colorimeter with a maltose solution of about the same concentration treated in the same way. The results were expressed as maltose and calculated to starch equivalent, 1 gm. of maltose hydrate being equivalent to 0.9 gm. of starch.

Another 5 c.c. portion was treated with 1 c.c. of saliva, incubated at 40 degrees C. for twenty-four hours, and the reducing sugar determined as before. The value obtained expresses practically complete digestion as far as amylase is concerned and the percentage of digestion of starch was calculated by using the reduction values thus obtained as a basis. Starch was, however, also determined in a number of cases by acid hydrolysis and titration of glucose formed, 10 per cent higher values were obtained for total starch in this way presumably because the small amounts of resistant dextrins left by the amylase are hydrolyzed by the acid. Results are therefore also expressed as percentages of the total starch converted to maltose.

Iron was determined in the third aliquot by adding an equal volume of concentrated hydrochloric acid, allowing it to stand over night, adding a little acid extracted blood charcoal, filtering, and taking a 5 c.c. aliquot of the filtrate. This was treated with 2 c.c. of 2 per cent potassium thiocyanate and water to make 10 c.c. The red obtained was compared with that of a standard ferric salt solution treated in the

same way. The ratio of total starch to iron was determined for the original test foods and for each gastric specimen. If there is any appreciable separation of the solid from the liquid portions of the digestion mixture, the iron, being practically insoluble, will follow the undigested starch. The total original starch was calculated for each specimen from the iron content, and the percentage of digestion was calculated using this value as a basis, as well as the percentage determined on the basis of the direct determination of digestible starch. Had there been any great variations in the starch-iron ratios due to stratification of contents or absorption of maltose it would have been necessary to consider the digestion percentages obtained as representing the minimum rather than the actual degrees of digestion. Thus, in any case the degree of salivary digestion would not be overestimated. It will be noted, however, that the variations in the starch-iron ratio were not sufficiently great to affect the significance of the results. Therefore, under the conditions of this test, the iron index may with a fair degree of safety be dispensed with and the procedure correspondingly simplified. Thus, the determination may be made in the course of a gastric analysis using ordinary bread as a test meal, and the examination may be further restricted to the half-hour specimen as most significant.

It will be noted from the accompanying table that from 54 to 84 (average 76) per cent of the starch of the potatoes was converted to maltose during the course of normal salivary digestion, and that from 46 to 68 (average 59) per cent of the starch of bread was so converted. These figures leave out of consideration the fairly large proportion of soluble dextrans also formed so that the proportion of unaltered starch remaining is evidently small. Muller,¹ using rice mush as a test meal, found that from 59 to 80 per cent of the carbohydrate was rendered soluble and with four normal subjects on a bread test meal found from 50 to 77 per cent of the starch to be rendered soluble (less when the food was poorly masticated). It is evident, therefore, that if food is properly masticated a very considerable degree of starch digestion may be brought about by saliva.

Active amylase was observed after fifteen minutes in one of the six experiments on potatoes and three of the six experiments on bread, and in only one case in all was active amylase found at thirty minutes. That these findings are correct and that the method of sampling in general was quite adequate is shown by the uniformity of the results and especially by the failure to find any considerable maltose formation after the thirty minute period. Active amylase was found only when no free hydrochloric acid could be detected. It is evident that salivary digestion was generally at a standstill about fifteen minutes after the meal was finished and that the considerable degree of starch hydrolysis

obtained was due more largely to the high digestive activity of the saliva than to a prolonged period of action in the stomach

The extent to which the salivary enzyme may contribute to the intestinal digestion of starch is not yet definitely known. Obviously, if much intact saliva with its high amylolytic power reached the intestine it would be capable of supplementing to no inconsiderable extent the pancreatic amylase. Such would be the case in subjects showing marked hyposecretion of gastric juice and even under conditions of normal gastric secretion it is possible that some unaltered saliva may reach the intestine through the relatively empty stomach or be washed through by water. It is further possible that small amounts of amylase may be adsorbed by raw starch and thus partially protected from the destructive action of the gastric acid.²

It would appear to be sufficiently established by the work of many investigators that amylase is destroyed by very low concentrations of hydrochloric acid, much lower in fact than those found in normal gastric contents at the height of digestion. Nevertheless, Pastore³ has quite recently published observations indicating that salivary amylase may remain active in 0.12 per cent hydrochloric acid and is not destroyed by 0.25 per cent acid nor by 0.5 per cent acid in the presence of starch. Furthermore, we still find quoted in textbooks the observations of Roger⁴ that saliva inactivated by acid (or by boiling) may be reactivated by small amounts of added amylase and hence may be reactivated by pancreatic amylase in the intestine.

As a check on the conclusions of Pastore the following experiment was carried out:

Five cubic centimeters of saliva was added to 100 c.c. of 10 per cent soluble starch. After fifteen minutes the solution, which showed erythrodestrin but no starch, was neutralized, 10 c.c. of 1 per cent starch added and hydrochloric acid to make 0.05 per cent, then the whole was incubated for fifteen minutes at 40 degrees C. The solution was neutralized to litmus, reincubated, and tested at intervals for undigested starch. Starch was still present after forty-eight hours, although it should have disappeared in ten seconds if the salivary amylase had not been destroyed.

It is evident from this experiment that large amounts of starch and its digestion products do not protect salivary amylase from destruction.

² Maestrini, D. *Atti d. r. Accad. d. Lincei, Roma* **29** 391, 1920, *Chem. Zentralbl.* **3** 184, 1921.

³ Pastore, S. *Atti d. r. Accad. d. Lincei, Roma* **29** 271, 1920, *Chem. Zentralbl.* **3** 184, 1921.

⁴ Roger, H. *Compt. rend. Soc. de biol.* **62** 83, 1021, 1907, *Rev. gén. d. sc.* **18** 544, 1907.

Salivary Digestion in the Human Stomach

Subjects 1 to 6 received 100 gm of mashed potatoes, subjects 7 to 12 received 75 gm of bread

Number	Time of Fasting, Minutes	Gastric Contents After 15 Minutes					Gastric Contents After 30 Minutes					Gastric Contents After 45 Minutes				
		Free Hydrochloric Acid, per Cent	Completeness of Starch Digestion, per Cent			Total Starch Converted to Mal tose, per Cent	Free Hydrochloric Acid, per Cent	Completeness of Starch Digestion, per Cent			Total Starch Converted to Mal tose, per Cent	Free Hydrochloric Acid, per Cent	Completeness of Starch Digestion, per Cent			Total Starch Converted to Mal tose, per Cent
			Amylase	From Iron Ratio	Direct			Amylase	From Iron Ratio	Direct			Amylase	From Iron Ratio	Direct	
1	10	0.07	—	30	30	27	0.24	—	49	49	14	0.27	—	62	60	54
2	12	0.09	—	79	82	74	0.11	—	82	86	77	0.01	—	91	92	83
3	10	0.12	—	89	91	82	0.15	—	98	98	88	0.30	—	93	93	84
4	14	0	+	76	74	67	0.06	—	89	87	78	0.14	—	88	84	75
5	12	0	—	100	100	90	0.25	—	91	90	81	0.33	—	92	90	81
6	18	0.15	—	84	79	71	0.26	—	90	87	78	0.28	—	92	90	81
Average	13	0.07		76	76	69	0.18		83	83	74	0.22		86	85	76
7	18	0	+	73	74	67	0	+	66	67	60	0	+	70	71	64
8	21	0.07	—	46	52	47	0.05	—	51	57	51	0.11	—	60	61	55
9	17	0.01	—	57	57	51	0.01	—	61	65	59	0.10	—	55	51	46
10	12	0	+	47	49	44	0.07	—	52	56	50	0.11	—	61	60	54
11	15	0.04	—	75	68	61	0.07	—	61	59	53	0.09	—	62	63	57
12	18	0	+	72	74	67	0.02	—	76	76	69	0.02	—	74	75	68
Average	17	0.02		61	62	57	0.04		61	63	57	0.07		64	64	59

by acid and that the digestive power is in no measure regained by neutralization. The experiments of Roger were repeated as follows:

Five cubic centimeter portions of saliva were treated with equal volumes of 0.5, 0.25, and 0.12 per cent hydrochloric acid for two hours at 40 degrees C. The mixtures were neutralized to rosolic acid and diluted to 50 c.c. Ten cubic centimeter portions were placed in each of three flasks and in each of three other flasks 10 c.c. of water and 0.3 c.c. of a solution containing 0.3 per cent sodium chloride and 0.02 per cent disodium phosphate to approximate the electrolyte concentration of the saliva. One cubic centimeter of 1:100 saliva was added to each flask together with 50 c.c. of 2 per cent starch paste and all were incubated for one hour and forty minutes at 35 degrees. The maltose in each flask was accurately determined by iodine titration of reduced copper oxide.⁵ The number of milligrams of copper reduced was for the first three flasks 77.5, 58.7, and 58.1, respectively, and for the three control flasks 72, 81.2 and 69.6, respectively. These results show practically identical amounts of maltose formed although a pronounced difference would have been observed if even 1 per cent of the salivary amylase had been reactivated.

It is evident from this experiment that saliva inactivated by acid is not reactivated by amylase and that the findings of Roger were due to failure to consider the electrolyte concentrations of his digestion mixtures. We have shown the same thing to be true of Roger's experiments on boiled saliva. When electrolyte was supplied, as in the experiment just described, the digestion of starch to the achromic point required a shorter time (one and one-half hours) than when boiled saliva was added (one and three-fourths hours). There was no activation of boiled saliva.

Maxwell⁶ and Nakagawa⁷ have observed that the digestion of protein *in vitro* by artificial or natural gastric juice was delayed by starch but not by the products of starch hydrolysis, presumably because of adsorption of pepsin by the colloidal starch when this was present. The salivary digestion of starch may therefore promote the gastric digestion of protein.

In disease we may expect salivary digestion to be influenced by the quantity and digestive power of saliva secreted and by the motility and secretory power of the stomach. Obviously, in achylia salivary diges-

⁵ Sherman, Kendall, and Clark. *J. Am. Chem. Soc.* **32** 1087, 1910, *ibid.* **33** 1947, 1911, *ibid.* **34** 317, 1912.

⁶ Maxwell, L. A. I. The Relation of Salivary to Gastric Digestion, *Biochem. J.* **9** 323, 1915.

⁷ Nakagawa, T. The Relation of Salivary to Gastric Secretion, *Biochem. J.* **16** 390, 1922.

tion in the stomach will be undisturbed and will proceed to practical completion for this type of digestion. If the stomach possesses a bulky and highly acid residuum, such as sometimes found in ulcer with retention, or if the secretory response of the stomach is rapid salivary digestion will evidently stop sooner than it otherwise would. The observations of Muller, as well as our own, indicate that a rapid development of gastric acidity is not incompatible with a high degree of salivary digestion because if food is properly masticated and starch digestion allowed to proceed for fifteen minutes or so in the stomach almost as much starch is broken down as when digestion can proceed for a longer time. For this the high amylase concentration of saliva is responsible.

The amylolytic power of saliva in various diseases has been studied by Carles and Delmas-Marsalet,⁸ who found low values in cachectic states, such as tuberculosis, and higher values in ulcer, indicating some parallelism with gastric chemistry. Probably more significant than quantitative changes in amylase concentration are variations in quantity of saliva secreted, and lowered salivary secretion may be expected in conditions diminishing body secretions generally, including gastric secretion. A diminished salivary secretion naturally calls for a longer period of mastication and the use of foods, such as acid fruits, stimulating salivary flow may be helpful.

Mention should be made of the work of Strausz,⁹ who compared the digestion of food containing raw starch when masticated in the usual way and when introduced by stomach or duodenal tube, thus avoiding the influence of saliva. In cases of fermentative dyspepsia and of pronounced hypermotility of the stomach and intestines, he found less starch in the feces when the food was masticated. In other gastrointestinal disorders and in normal persons, no difference could be noted.

It must of course be borne in mind that the importance of the proper mastication of foods lies not merely in improving the ultimate utilization of starch. Comminution of food is of obvious importance. Mastication stimulates gastric secretion, which in turn stimulates pancreatic secretion. We may expect a more rapid utilization of foods, leaving less of these to pass into the lower bowel and become subject to bacterial action. Motor as well as secretory activities of the gastrointestinal tract are closely correlated, and disturbance of the initial digestive function may affect the whole digestive rhythm.

8 Carles, J., and Delmas-Marsalet, P. Variations du pouvoir amylolytique a la salive au cours d'etats pathologiques divers, *Compt rend Soc de biol* **91** 42 (June 13) 1924.

9 Strausz, L. Ueber den Einfluss der Ausschaltung des Mundspeichels bei Magen- und Darmkranken, *Arch f Verdauungskr* **33** 163, 1924.

SUMMARY

1 The extent of salivary digestion of the starch of a test meal may be determined in the course of a gastric analysis, using the retention stomach tube

2 Bread or other foods containing a known amount of iron oxid may be used in studies of gastro-intestinal digestion and absorption, iron determinations serving as a guide in interpretation of the results

3 Studies of salivary digestion in the stomachs of normal men showed on the average 76 per cent of the starch of mashed potatoes and 59 per cent of the starch of bread to be converted to maltose, an additional percentage being changed to dextrins

4 This considerable degree of starch conversion was generally brought about within from fifteen to thirty minutes after the meal was finished, active amylase disappearing and free hydrochloric acid appearing simultaneously

5 Salivary amylase is inactivated by low concentrations of free hydrochloric acid even in the presence of starch and its digestion products and does not again become active when the acidity is neutralized. Neither is it possible to reactivate, by the addition of small amounts of active amylase, saliva that has been inactivated by acid or by boiling. To function in the intestine saliva must escape the action of acid gastric juice

PARALLELISM IN THE TREATMENT OF TUBERCULOSIS AND CARDIAC DISEASE

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The outstanding and gratifying phenomenon in the eradication of chronic disease—the decline in the tuberculosis death rate during the last two decades—invites serious attention to the malady that has supplanted tuberculosis as “captain of the men of death.” Although tuberculosis still ranks among the major killing diseases and is exceeded only by heart disease and pneumonia, its past steady decrease is an almost certain augury of continued lessening of its menace and suggests that we be prepared, as tuberculosis becomes a less grave problem, to place in the campaign against the new “captain of death” as many as possible of the resources with which we have successfully fought the old.

The cut of more than half in tuberculosis mortality during the last twenty years brings into sharp contrast the situation with respect to mortality from heart disease, which has increased 31 per cent in the United States during approximately the same period. This increase has been gradual and steady, with only one notable interruption, following the influenza epidemic of 1918, when the death rate in the United States dropped from 153.3 per hundred thousand in 1918 to 131 per hundred thousand in 1919. In 1900 the death rate from heart diseases in the registration area of the United States was 111.2 per hundred thousand. For the same area in 1922 the death rate was 148.4, and for the registration states in 1923 the rate had increased to 162.2. This rate includes all ages for both colored and white.

There are certain known and obvious causes of heart disease. The acute infectious diseases of children—acute rheumatic fever, chorea and scarlet fever—are notable for the frequency and manner in which they affect the heart. In the first three decades of life acute rheumatic fever is the most prominent causative factor. From the third decade on syphilis is an increasing cause of mortality, while in midlife the so-called degenerative diseases are the commonest cause of cardiac illness.

MORTALITY AT DIFFERENT AGE PERIODS

At all age periods of life cardiac disease is prevalent and crippling. After the fifth year in childhood the mortality rate steadily increases. At the age period from 10 to 14 the death rate from heart disease, in the experience of the Metropolitan Life Insurance Company among

twenty-four million industrial policyholders, exceeds the combined death rates for the four principal diseases of childhood, and is surpassed only by tuberculosis. At the ages from 35 to 44 one white person in every thousand living dies of heart diseases, while at the ages from 55 to 64 six of every thousand living die of cardiac disease. Among colored people the death rate is higher than among whites, in the company's experience the colored death rate averaging about twice as high as for whites at the age periods from 25 to 54.

TABLE 1—*Death Rates Per Hundred Thousand for Organic Diseases of the Heart in the U S Registration Area from 1900 to 1923*

Year	Death Rate per Hundred Thousand	Year	Death Rate per Hundred Thousand
1923	162.2*	1911	141.1
1922	148.4	1910	141.5
1921	140.9	1909	129.7
1920	141.9	1908	128.3
1919	131.0	1907	137.5
1918	153.3	1906	127.6
1917	153.8	1905	131.3
1916	150.6	1904	133.4
1915	147.6	1903	124.5
1914	142.2	1902	117.3
1913	138.9	1901	113.4
1912	142.8	1900	111.2

* Registration states

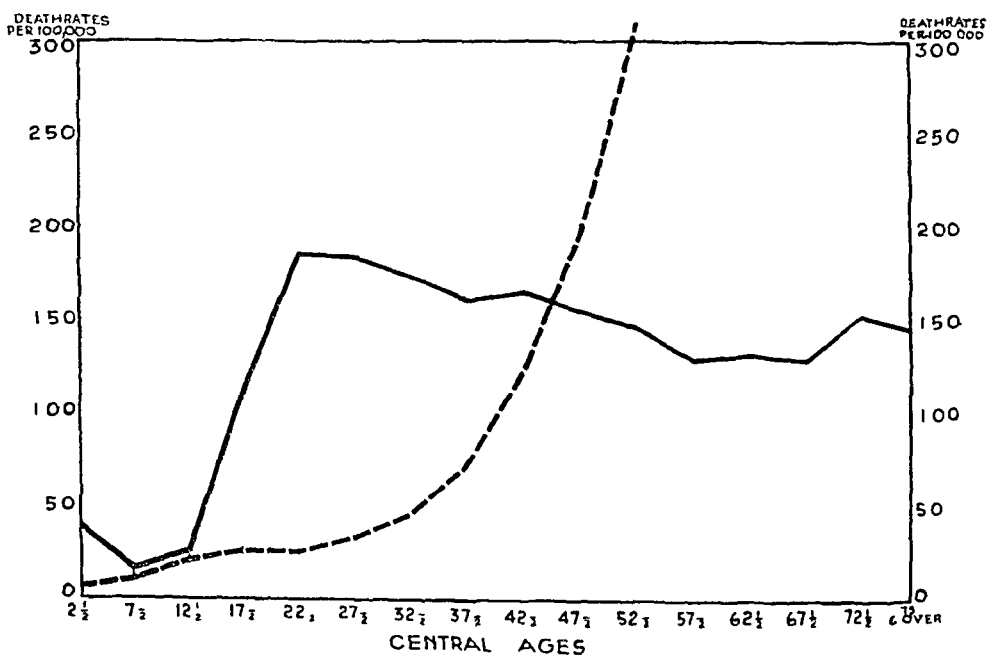
TABLE 2—*Death Rates Per Hundred Thousand for Organic Diseases of the Heart in the Metropolitan Life Insurance Company Industrial Department for 1923 by Color, Sex and Age and in the Registration States for 1922 by Sex and Age*

Age Periods	Metropolitan Life Insurance Company Industrial Department				U S Registration States	
	White		Colored		Males	Females
	Males	Females	Males	Females		
All ages	112.2	120.9	189.6	216.1	151.2	146.5
Under 5	7.7	6.6	20.7	11.0	10.6	9.4
From 5 to 9	10.3	10.8	17.5	10.8	8.8	9.6
From 10 to 14	19.8	23.2	28.9	16.0	13.7	16.8
From 15 to 19	27.6	23.9	28.4	19.3	18.3	18.7
From 20 to 24	23.9	25.2	27.6	38.1	18.2	20.3
From 25 to 34	39.6	32.4	68.0	58.7	25.2	29.8
From 35 to 44	86.6	70.7	180.3	184.7	59.6	63.1
From 45 to 54	253.3	184.9	424.6	470.4	167.1	159.3
From 55 to 64	681.3	535.6	831.9	948.8	447.9	396.2
From 65 to 74	1,719.9	1,545.4	1,595.6	1,641.1	1,210.1	1,118.6
From 75 and over	4,060.8	3,524.7	2,600.1	3,016.5	3,105.9	2,969.1

Contrasting the age periods at which heart disease and tuberculosis cause the greatest mortality, it will be seen that tuberculosis still holds first rank from the ages 20 to 40, while heart disease becomes the leading cause of death soon after the age of 40. And so great is the increase thereafter that in totality heart disease exceeds every other. In the company's industrial experience for 1923 the rising curve of heart mortality crosses the declining curve of tuberculosis mortality at the age of 45.

Thus, cardiac disease has come to be a seriously fatal factor in our economic life, sweeping off great numbers of persons at the height of their productiveness, and the extent of the problem is not fully revealed in tables showing the mortality from heart disease since there are great numbers of deaths each year, especially in the midlife periods, from apoplexy, nephritis and other diseases in which the heart is vitally affected and may be the cause of death

While much work has been done and experience gathered to reveal the morbidity incidence of heart disease, as yet we have no completely satisfying data. There is available, however, the record of school inspections which show that 2 per cent of school children examined have heart impairments of various kinds. If we may conservatively consider that 1 per cent of the 30,000,000 school children in the United



Comparative death rate per hundred thousand in patients with tuberculosis and with heart disease in the industrial experience of the Metropolitan Life Insurance Company in 1923—solid line, tuberculosis, broken line, heart disease

States are affected by heart disease, we can begin to realize the enormity of the problem affecting 300,000 children of school age who will carry this serious debility throughout their precarious lives

As a gage of morbidity among adults we have the draft examinations of the Great War, which gave 2.6 per cent rejections for heart disease among men from 21 to 31 years of age. The experience of the Metropolitan Life Insurance Company gives a rejection for heart disease of 2 per cent of those examined each year. From these widespread examinations representing a cross section of our young adults in the case of the draft, and a large group of adults applying for insurance

in the case of the company, we may safely conclude that approximately 1,500,000 adults in the United States are affected by heart disease of such seriousness as to unfit them for heavy military duty or as sound insurance risks.

Whether the causes of these impairments be started in early life by acute infectious diseases, whether they be produced later by syphilis, or whether they fall within the wide range of degenerative conditions of midlife, the fact is that there are now about one-fiftieth of our people who are ill, or will become ill, of heart disease, and whose mortality will lead all the rest of the brigade of death.

RECENT VIEWS OF SCIENTISTS AND CLINICIANS

The intensive study of heart disease within recent years by scientists and clinicians has modified and advanced our views concerning the nature of these ailments, and has emphasized the serious threat of heart disease at various periods of life. Through studies made in cardiac clinics, dispensaries and hospitals we have learned much that is now known of the life history of the cardiac patient. The statistical data that have been brought together and studied during this period have brought above the horizon many important facts respecting the mortality from heart disease in various periods of life and the seriousness of the situation as it exists at present. Unlike tuberculosis, the cardiac problem lacks the fear of infection and the consequent articulate demand by the profession and the public for segregation, this increases the difficulties of arousing general interest to its seriousness. Unfortunately, at present the cardiac patient rarely comes under observation in his home or in the dispensary or hospital, except when his symptoms are pronounced enough to interfere with his work or pleasure, and it is a common experience to find decompensation advanced to a point where symptoms are so severe as to interfere with his ability to undertake any productive activities. Naturally the future of such patients is precarious. The failure of their circulatory system is so pronounced that rehabilitation is greatly limited, if not impossible, and for a considerable part they drag out a dreary and shortened existence.

From a practical clinical standpoint we may divide patients with heart diseases, as we see them, into three classes: patients whose symptoms are of a mild nature and whose usual activities are interfered with only slightly, if at all; patients in whom symptoms have become more pronounced and are brought about more frequently and by less strain but who are yet able to maintain a moderate normal activity, and patients whose symptoms cause distress of various kinds which inhibits or wholly prohibits any physical activity. We have at present little appreciation of the earliest evidences of adult heart disease, notwithstand-

ing the great amount of study that is being given to this important problem. In many instances it is not difficult to trace symptoms back to early and milder stages of the disease which have progressed for months, or many years, with gradually increasing intensity, until the crippling breaks begin to appear. There are still woful gaps in our knowledge of the life history of cardiac patients owing, in part at least, to the present lack of facilities for concerted and prolonged study of these cases, indeed, there is no experience available that is comparable with the prolonged studies that have been made respecting the beginning and the course of tuberculosis.

It seems really doubtful whether any great progress can be made in the intelligent handling of this problem until we know more of the various factors that enter into the making and treating of the cardiac patient. At present there are few places outside of the home to which the cardiac patient can go for such prolonged treatment as he requires. The hospitals and dispensaries of the country are obviously inadequate in space for the care of these patients, whose observation and treatment should be prolonged for periods of weeks or months, and should contribute to the building up of a life history of the disease. So far as possible all etiologic factors, both physical and mental, should be searched for and corrected. Our present conception is that while there are general laws respecting the care and treatment of cardiac patients it is understood that there is no single standard, or group of standards, by which we can gage cardiac capacity. The treatment of heart disease, therefore, requires detailed individual study and testing of the patient before it can be known what powers for recuperation are available. Quite generally the cardiac patient has associated diseases that may be causative or resultant. On their recognition and treatment success or failure often depend. The syphilitic patient with his aortitis and secondary heart impairment is obviously unhelped unless his specific infection is minimized by treatment. When nephritis is associated with or underlies heart disease it, too, must have proper and continued treatment.

For the rehabilitation of the modern cardiac patient there is required a study of his past, observation of his present, and an estimation of his future capacities.

ADAPTABILITY OF TUBERCULOSIS SANATORIUMS FOR TREATMENT

The personnel and equipment of the modern tuberculosis sanatorium are peculiarly well adapted to the treatment of heart disease. Obviously there is lacking in heart disease the urge for segregation of the patient that has been so successfully employed in tuberculosis because of its infectiousness, and yet separation of the cardiac patient from the

environment in which he got sick is often quite as important from the standpoint of recovery as it has proved to be in the treatment of tuberculosis. To remove him from the usual worries and stresses in the home may be the first assured step in his convalescence. In our experience in the treatment of a large group of cardiac patients the elements of nostalgia and distress of separation from home have been no more prevalent or aggravating than in the tuberculous subject. The initiation and pursuit of a restorative regimen are comparatively easy and certain in an institution. The elements of cooperation and example, so helpful in the treatment of tuberculosis, are quite as potent and available in the care of cardiac patients. The average cardiac patient with mild or moderate symptoms should receive quite prompt and lasting benefit from the kind of treatment that can be supplied in tuberculosis sanatoriums.

Specifically the cardiac patient requires rest in bed. No remedy equals it. And the rest must be prolonged and observed. Only through persistent and sustained rest can recuperation begin. While resting the patient offers the required opportunity for study and the gathering of needed information of his physical disability, its nature and extent, and whether his circulatory system has ability to respond to treatment. This period of rest affords occasion for bringing together fragments of history that will form the pictorial background of the patient and will lead eventually to the accumulation of essential information of the life history of the cardiac patient.

Examination of the urine and blood is, of course, essential, and in many cases the determination of the chemistry of the blood and the renal function is required for the complete understanding of the diseased heart. Clinical instrumentation, including the use of the polygraph and the electrocardiograph, is helpful in differentiating various kinds and degrees of heart impairments.

When rest has served its purpose exercise is utilized to restore tone and efficiency to the circulatory apparatus and the body. Through exercise, graduated and controlled as to time, character and amount, one learns the physical capacities of the subject and to what extent he can adapt himself to a normal life. All the forms of occupation and exercise that have been employed in the tuberculosis sanatoriums are available and useful to restore the cardiac patient. Occupational therapy in its many forms has proved especially beneficial to the cardiac patient, both in bed and when ambulant. Walking controlled by distance rather than by time, is a potent form of restorer to a weakened myocardium. Subsequently, and when restoration has been well established, more arduous forms of exercise may be employed, and especially in the milder cases.

In cardiac patients with associated nephritis diet becomes an important feature in the treatment. In many cases of midlife heart disease, overweight is a prominent associated factor—if not a causative one—and the reduction of the weight over a period of time requires careful dieting and guidance that the heart may not be further impaired. The provision of proper diet for the cardiac patient is quite within the possibility of any tuberculosis sanatorium, indeed, the facilities at present available in sanatoriums are ample to supply the required remedial agents in heart disease. No one knows better than the tuberculosis specialist the value and methods of administering rest, indeed, that has been the essence of success in recovery from tuberculosis, and the methods are thoroughly established. The careful prescribing of exercise to the tuberculous subject has been second only in importance to the value of prolonged rest, and the gradual restoration of strength through exercise has been amply experienced by all who have guided the convalescence of tuberculous persons.

Baths have been extensively used in spas in the treatment of some forms of cardiac diseases, and such baths as may be thought helpful can be readily and inexpensively reproduced in any institution.

Possibly the one outstanding objection to the treatment of heart disease in a tuberculosis sanatorium would be the fact that most sanatoriums are constructed largely to provide a maximum of out of door life, and obviously many cardiac patients cannot be treated out of doors in cold weather. Several modernly planned sanatoriums have aimed to provide a maximum number of enclosed rooms to permit isolation of tuberculous patients. In others, and this seems to be the modern trend, enclosed porches have been provided. In many institutions it would be possible to increase the number of heated rooms and wards, and this, without undue expense, would permit the care of any type of cardiac patient. Many patients with the early and milder forms of heart disease are not jeopardized by out of door life, especially in the warmer seasons, indeed, they are benefited by exposure to the open air. The types of heart disease requiring a uniformly mild atmosphere are those of badly broken compensation and those having an associated serious nephritis.

Moderate altitudes are not prejudicial to the treatment of cardiac subjects and it can be safely said that most such cases are not embarrassed at heights up to 1,500 feet.

CARE OF PATIENTS IN METROPOLITAN LIFE INSURANCE COMPANY SANATORIUM

Firmly believing in the suitability of the modern tuberculosis sanatorium for the treatment of heart disease, the Metropolitan Life Insurance Company in its Sanatorium at Mount McGregor, has for

several years cared for patients with these diseases as they have been recognized among the company's staff of employees. Ever since the dedication of the sanatorium in 1913 nontuberculous patients have been treated, but the majority of cardiac patients have been admitted during the last six years. Up to Dec 31, 1924, 1,778 nontuberculous patients were admitted, of whom 440, or 24.7 per cent, had heart and arterial diseases. As employees of the company, the patients included only adults, and 26 per cent of the cardiac patients were between the ages of 20 and 39, while 59 per cent were in the age groups from 40 to 59, 13 per cent were more than 60. Obviously this experience is not concerned with heart disease in children per se, but as the diseases of early years may be reflected into adult life.

The facilities for treatment are in the main similar to those found in most tuberculosis sanatoriums, consisting of an infirmary and open ward buildings. In addition there is one building with forty-seven beds in which prolonged treatment is given to patients with serious cardiac

TABLE 3—*Primary Diagnoses and Complications in Arterial and Heart Diseases*

	Males		Females		Both Sexes	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Total	330	100.0	82	100.0	412	100.0
Under 20 years	1	0.3	6	7.3	7	1.7
From 20 to 39 years	55	16.7	53	64.7	108	26.2
From 40 to 59 years	221	67.0	23	28.0	244	59.2
From 60 to 79 years	53	16.0	0	0	53	12.9

disease and to others. This building is similar in its plan to the general type of infirmary, save for the lessened porch space and the provision of rooms for one and two patients. Patients with the milder forms of cardiac disease and those without serious complications are treated in open wards.

From the standpoint of etiology the arterial sclerotic patient made up the largest class of patients treated. They comprised 46 per cent of the total number and were found mainly beyond 40 years of age, often overweight, and many having high blood pressure and nephritis. These cases fall within the large general group of midlife degenerative diseases. The rheumatic patients formed 16 per cent of the group treated, while the syphilis patients made only 3 per cent of the group.

The general plan of treatment provides for complete bed rest of every admitted patient until the essential examinations have been made, the period of rest depending on the condition of the vascular system and the patient's response to treatment. In the sanatorium the period of bed rest has averaged forty-four days. The patient's physical resources are tested gradually to determine the limits within which he can exercise

without danger This period of graduated exercise is continued persistently until it is demonstrated either that the vascular system has not enough resources to enable the patient to resume work, or until he can take up an occupation

PRESENT CONDITION OF PATIENTS

Up to Dec 31, 1924, 412 cardiac patients had been discharged from the sanatorium The average period of treatment for this entire group was four months and twenty-six days Briefly, the present condition of this group of patients is as follows

Of the 412 patients, 198, or 48 per cent, are able to do full time work, thirteen, or 3 2 per cent, are carrying on modified work, 109, or 26 4 per cent, are unable to work, and seventy-nine, or 19 2 per cent, are dead We were unable to trace thirteen, or 3 2 per cent, in time to incorporate their condition in this article Many of these patients who are now working have undoubtedly been restored to full powers and efficiency through treatment in the sanatorium They have had the

TABLE 4—*Present Condition of 412 Patients with Heart Disease Discharged Up to Dec 31, 1924*

		Per Cent
Able to work	198	48 1
Able to do modified work	13	3 2
Unable to work	109	26 4
Dead	79	19 2
Unable to trace	13	3 1

required rest and exercise, have learned to adjust themselves to their impairment, and have acquired an experience in cardiac illness which enables them to keep well within their physical limitations in the stresses of a reasonably normal life As in the treatment of tuberculosis so in heart disease, the great accomplishment is to teach the patient to accommodate himself to his disability And yet these figures show more clearly than anything I can say the present serious state of the cardiac patient In our studies and examinations of a circumscribed group of more than 30,000 employees working throughout the United States and Canada, we are making a serious effort to find the early cardiac patient We have come to appreciate the difficulties in the way of bringing our cardiac patients under treatment when the best rehabilitation is possible and only now are we beginning to see the results of this effort Somehow notwithstanding its calamitous ways, heart disease has seemed to lack the threat that tuberculosis has held for the public for many years But gradually this considerable group is beginning to appreciate the prevalence of heart disease and its crippling nature They are learning

what every one must learn—that heart disease brings prompt and almost certain reduction in earning capacity and economic usefulness as well as enjoyment of life

From this isolated and quite novel experience the treatment of heart disease in a tuberculosis sanatorium has been demonstrated as possible and satisfactory. To the patient has come an opportunity, similar to that provided the tuberculous patient, to acquire the maximum recovery of which his organism is capable, to learn his physical capacities and limitations, and, most important, to prepare for his adjustment to the environment in which he lives and works. In the study and treatment of the cardiac patient, there awaits the physician whose interests have been centered on chest diseases a new medical interest, stimulating, absorbing and rewarding.

THE VITAL CAPACITIES OF ONE THOUSAND SURGICAL PATIENTS^{*}

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ROCHESTER, MINN

The function of respiration has commanded the attention of physicians from the earliest history of medicine, and many fascinating theories were expounded in ancient times to explain it. Galen probably was the first investigator to have an approximately correct conception of its purpose. Nevertheless, for 1,500 years or more, the truths he advocated were disputed and submerged by superstition. It may be safely stated that the first great epoch in our knowledge of respiration began with the investigation of the circulation by Harvey and the publication of his first work in 1628. It was about two centuries later that studies were made on the vital capacity of the lungs and, while studies had been previously made, it was not until the appearance of the classical monograph by Hutchinson¹ in 1846, "On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer," that its study was placed on a sound basis. The more one studies this classical article, the more one realizes that what we know today regarding vital capacity of the lungs was either established or foreshadowed by him. The minuteness of his observations, the multitude of tests and the great care he exercised in establishing normals to check his observations may well serve as a model for scientific work today. His closing remarks reveal his modesty and restraint.

The matter of this communication is founded upon a vast number of facts—immutable truths, which are infinitely beyond my comprehension. The deductions, however, which I have ventured to draw therefrom, I wish to advance with modesty, because time, with its mutations, may so unfold science as to crush these deductions and demonstrate them as unsound. Nevertheless, the facts themselves can never alter nor deviate in their bearing upon respiration—one of the most important functions in the animal economy.

In recent years, especially since 1917, there has been a general revival of interest in the study of vital capacity. This renewed interest is primarily¹ due to the work of Peabody and Wentworth² of this

^{*} From the section on medicine, Mayo Clinic.

^{*} Abridgment of thesis submitted to the faculty of the University of Minnesota Graduate School of Medicine in partial fulfillment of the requirements for the degree of master of science in medicine, March, 1925.

1 Hutchinson, John. On the Capacity of the Lungs, and on the Respiratory Functions, with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, *Tr Med Chir* **39** 137-252, 1846.

2 Peabody, F W, and Wentworth, J A. Clinical Studies of the Respiration, IV, The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch Int Med* **20** 443-467 (Sept) 1917.

country and Dreyer³ of England. The literature on the subject since 1917 has become extensive, both from the clinical and the investigative aspects, and has been chiefly concerned with the determination of the normal capacity. The objection to the majority of observations is that they are made on healthy young college students and then applied to every age and walk in life.

In order to secure a wider and better conception of the value, applicability and accuracy of determinations of vital capacity, and the influence of diseases not involving external respiration, it was decided to make observations on a more heterogeneous group of persons. Accordingly observations were made on 1,000 consecutive adult patients who came for surgical treatment to the Mayo Clinic, irrespective of age, occupation, sex, stature, degree of physical fitness or walk of life.

TECHNIC

The spirometer used in making the determinations in this study was of the wet type and especially constructed at the Mayo Clinic (Fig. 1). By means of this instrument it is possible to determine within 8 c.c. the amount of air expired. It is so delicately balanced that the slightest inspiration is recorded on the scale. A spring cock valve at the opening into the tank permits control of the intake or outlet of air at any point in the respiratory cycle. The mouthpiece of the instrument is of nickel, may be easily and rapidly sterilized, and is so constructed that it can be held in the mouth firmly enough to prevent leakage. The subjects were instructed to inspire and expire as deeply as possible, to keep the nose closed, and to expire at a fairly uniform rate, thus preventing any possible escape of air around the mouthpiece. A nasal slip was not used because patients frequently complained that it annoyed them. When there was leakage around the mouthpiece it was easily recognized by the fogging of the nickel.

The following measurements and facts were determined for each patient: age, sex, place of residence, height, weight, body surface and vital capacity, as well as the disease. The height was measured without shoes and the weight was determined without clothing. From three to five, and even more, determinations of vital capacity were made in each instance, the highest always being accepted. All patients were subjected to a complete and thorough physical examination.

All readings of vital capacity were made in the middle of the morning, with extraneous influences reduced to a minimum when possible. Friends and relatives were excluded from the room, especially in the case of women, as their attention seemed to be easily distracted from the test.

³ Dreyer, Georges. The Normal Vital Capacity in Man and Its Relation to the Size of the Body, *Lancet* 2: 227-240 (Aug. 9) 1919.

EXTRINSIC FACTORS INFLUENCING VITAL CAPACITY

Many investigators wish to discard the spirometer because of the difficulty in interpreting the readings. Furthermore, they advance the argument that even when the readings are interpreted correctly, they do not determine the nature or even the existence of disease. On

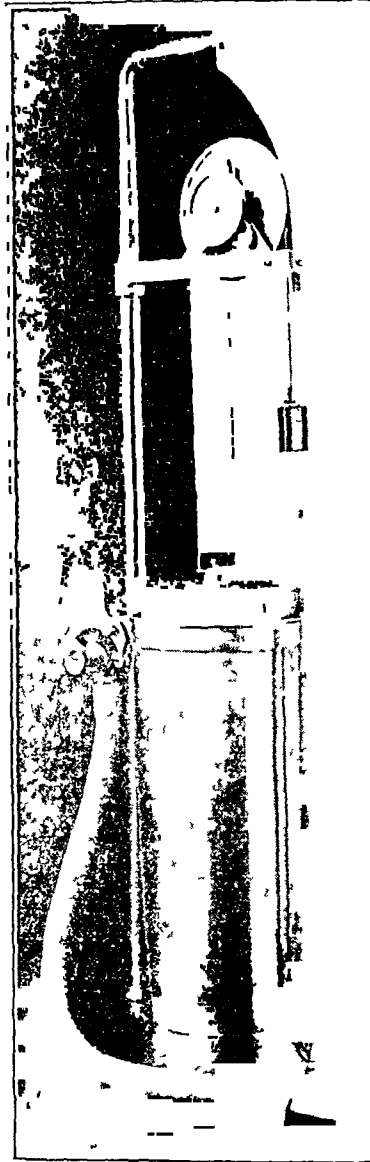


Fig 1—Spirometer used in work reported

similar grounds there would be no justification for the recording of temperature, pulse rate or number of leukocytes. As a reduced vital capacity warns us that disease is present, especially in the heart and lungs, the use of the spirometer is as justifiable as that of the thermometer, blood pressure apparatus or blood counting chamber.

Posture—Among the various extraneous influences that must be considered are posture, season, temperature, atmospheric pressure, and race. The importance of position is shown if one accepts the dictum that vital capacities of 10 per cent below the calculated normal indicate a pathologic state. Christie and Beams⁴ found that the vital capacity taken in a reclining position averaged 5.5 per cent below that taken in the sitting position. Peabody⁵ asserts that the vital capacity should be taken with the subject either standing or sitting erect, as it is usually from 200 to 300 c.c. lower than when taken in the horizontal position. Rabinowitch,⁶ in a series of fifty normal subjects, studied to learn the influence of posture, found a decrease in vital capacity varying from 20 to 600 c.c., and a mean decrease of 7.5 per cent when they were in the recumbent position. Rubow⁷ and also Hasselbalch⁸ found that the vital capacity was greater in the standing than in the sitting position. On account of this variation, all the readings to be given were taken with the subject standing.

Time of Last Meal—Hutchinson found that a full meal before the determination might decrease the vital capacity 200 c.c., or even as much as 38 c.c. Wittich, Myers and Jennings,⁹ however, believe that a full meal does not exert an appreciable effect on vital capacity. I have seen reductions as great as 200 c.c. after a heavy meal, and believe the reduction is partially due to decreased effort associated with the discomfort of forced expiration when the abdomen is distended. After meals of moderate size, the variation is usually slight or absent.

Psychic Influences—The psychic factor, as in many tests, is so variable an element, especially among female subjects, that it is difficult to estimate it. The least disturbance during the test caused in most instances a decided decrease in vital capacity. A certain group of middle-aged women apparently take pride in being considered below normal physically and do not put forth their best efforts. It is there-

4 Christie, C. D., and Beams, A. J. The Estimation of Normal Vital Capacity, with Especial Reference to the Effect of Posture, *Arch Int Med* **30** 34-39 (July) 1922.

5 Peabody, F. W. The Clinical Importance of the Vital Capacity of the Lungs, *Northwest Med* **22** 307-311 (Sept.), 350-352 (Oct.) 1923.

6 Rabinowitch, I. M. The Vital Capacity in Hyperthyroidism with a Study of the Influence of Posture, *Arch Int Med* **31** 910-915 (June) 1923.

7 Rubow, V. Untersuchungen über die Atmung bei Herzkrankheiten, Ein Beitrag zum Studium der Pathologie des kleinen Kreislaufes, *Deutsch Arch f klin Med* **92** 255-281, 1908.

8 Hasselbalch, K., quoted by Haldane, J. S. Some Recent Advances in the Physiology of Respiration, Renal Secretion and Circulation, *Brit M J* **1** 409-413 (March 19) 1921.

9 Wittich, F. W., Myers, J. A., and Jennings, F. L. A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, *J A M A* **75** 1249-1252 (Nov 6) 1920.

fore necessary to try to eliminate these influences as far as possible. While certain persons are stimulated to greater effort by the psychic influence of competition, others show the opposite effect. Men especially seem to do better under the stress of competition. This was demonstrated by the following experiment. Six men were examined individually and the readings noted. Then they were all admitted to the same room at the same time and a contest instituted to see who could do the best. The previous readings were increased by several hundred cubic centimeters in all but one case.

INTRINSIC FACTORS

In spite of many and diversified formulas of normal variation advocated, it is improbable that any one will ever be evolved that can be regarded as normal for all persons, but if the various modifying factors, both intrinsic and extrinsic, are taken into consideration, a standard of normal variation will prove very useful. One objection to most standards is that they were based on studies of young healthy persons, in most cases with exceptional advantages for superior development. To advocate an arbitrary point below which everything could be regarded as pathologic indeed seems unjustifiable, as even among the normal persons a certain group falls below the usually advocated normal limit of from — 10 to 15 per cent. Myers and Myers,¹⁰ in a study of 1,280 men at the University of Minnesota between the ages of 17 and 32, and 1,058 young women at the same institution, found 11.4 per cent of the men and 27.1 per cent of the women below 85 per cent of their estimated normal vital capacity. While they ascribe the low readings to disease in the chest, inaccuracy of the normal standard and errors in recording, it would seem that the arbitrary normal is not applicable to all, but that each individual case must be considered separately.

The class of patients presented in this paper was therefore selected in preference because they represent something of a cross section of the human family. While it is true that they represent the diseased class, still I feel that it is a more representative group than a body of college students mostly in one period of life.

Sex—Probably one of the most striking influences is that of sex. Hutchinson mentioned it as one of the four chief factors that influence vital capacity. Practically all formulas advocated for the estimation of vital capacity take this factor into consideration and make due allowance for the difference. On the average the capacity of men is about 20 per cent higher than that of women. In children, as pointed out by

¹⁰ Myers, J. A., and Myers, F. J. Studies on the Respiratory Organs in Health and Disease, IX, The Vital Capacity in a Group of College Men, *Journal-Lancet* 43 276-277 (June 1) 1923.

Wilson and Edwards,¹¹ the difference is about 37 per cent. I have no figures to prove or disprove variations due to menstruation, and I have found none in the literature. Wittich, Myers and Jennings, however, found that pregnancy has no influence on the readings and although their group is small, their conclusions are well supported.

Age—Hutchinson mentioned age as one of the chief factors influencing vital capacity but felt that it had less bearing than either height or weight. He stated that it increased up to the age of 30, and from 30 to 60 it decreased 43 cu in., or 1.43 cu in. a year. It is of interest to keep these figures in mind in relation to the variations found in the present group. Dreyer³ asserts that age has little influence on vital capacity before the age of 50. Peabody and Wentworth,² Myers¹² and others have come to a similar conclusion. Bowen¹³ believes that after fifty years there is a distinct gradual decrease, reaching 50 per cent at the age of 85, the greatest drop occurring between 50 and 60. Pratt,¹⁴ in a study of 100 normal men, concluded that the period of greatest

TABLE 1—*Variation in Vital Capacity in One Hundred Normal Men According to Age (Pratt)*

Age, Years	Males	Average Vital Capacity, C c	Surface Area, Sq. M	Percentage Variation from Normal Surface Area (West's Formula)
10-20	9	3,125	1.47	-18.0
20-30	14	4,500	1.72	+5.0
30-40	23	3,950	1.75	-10.0
40-50	20	3,775	1.81	-17.0
50-60	20	3,825	1.85	-17.0
60-70	11	3,300	1.80	-27.0
70-80	3	2,525	1.82	-44.0

capacity was in the third decade but that capacity did not fall much until the age of 60 (Table 1). The striking fact in Pratt's series is that in the aged the body surface was greater than in youth, while the height remained much the same, indicating greater weight for the same height, therefore obesity would be an associated factor in the decrease with age.

In classifying 1,775 males according to age, Hutchinson obtained the results in Table 2. The influence of age, as observed in this study, is in fairly close harmony with that observed by Hutchinson and is presented in Table 3 for comparison. For the sake of convenience and better evaluation, the cases are divided into two groups on the basis of sex.

11 Wilson, May G., and Edwards, D. J. Diagnostic Value of Determining Vital Capacity of Lungs of Children, *J. A. M. A.* **78** 1107-1110 (April 15) 1922.

12 Myers, J. A. Studies on the Respiratory Organs in Health and Disease, III, The Value of Vital Capacity Readings in Clinical Medicine, *Minnesota Med.* **4** 635-640 (Nov.) 1921.

13 Bowen, B. D., and Platt, D. L. The Relation of Age and Obesity to Vital Capacity, *Arch. Int. Med.* **31** 579-589 (April) 1923.

14 Pratt, J. H. Long-Continued Observations on the Vital Capacity in Health and Heart Disease, *Am. J. M. Sc.* **164** 819-832 (Dec.) 1922.

The variation between the ages of 20 and 60 is fairly uniform in all three groups. Between the years of 60 and 70, Pratt's figures would tend to show a rather sharp decrease in vital capacity as compared with my series. It may be said that there is a gradual decrease in vital capacity after the fourth decade and a more noticeable decrease after the fifth decade. With increasing age the number of persons with capacities above normal decreases, whereas the reverse is true with regard to persons with capacities below normal. Lemon and Moersch¹⁵ and Arnett and Kornblum¹⁶ have called attention to the fact that age must be con-

TABLE 2—*Variation in Vital Capacity in One Thousand Seven Hundred and Seventy-Five Men According to Age (Hutchinson)*

Age, Years	Males	Average Vital Capacity, C c
15-20	283	3,608
20-30	838	3,624
30-40	413	3,633
40-50	148	3,272
50-60	67	3,084
60-65	26	3,001

TABLE 3—*Variation in Vital Capacity According to Age in Four Hundred and Eighteen Males and Five Hundred and Eighty-Six Females with Number and Percentage Variation from Estimated Normal (West's Formula)*

Age Years	Number	Average Vital Capacity, C c	Males				Variation and Number Above and Below Estimated Normal Vital Capacity According to Surface Area			
			Variation and Number Above and Below Estimated Normal Vital Capacity According to Height				Variation and Number Above and Below Estimated Normal Vital Capacity According to Surface Area			
			Number	Plus	Number	Minus	Number	Plus	Number	Minus
15-20	4	5,019	3	21.6	1	8.0	3	16.0	1	9.0
20-30	58	4,759	44	16.4	14	10.4	46	13.0	2	10.4
30-40	111	4,608	83	14.1	28	12.6	75	12.2	36	13.1
40-50	122	4,422	71	11.5	51	9.8	61	10.5	61	11.0
50-60	86	4,215	44	12.9	42	15.5	40	10.1	46	17.0
60-70	35	4,071	12	11.0	23	12.6	8	8.5	27	14.5
70-80	2	3,958	1	3.0	1	11.0	1	0.0	1	15.0
Females										
15-20	9	2,689	2	11.5	7	18.1	5	6.3	4	18.5
20-30	103	3,088	42	11.3	61	14.7	55	10.3	48	13.3
30-40	157	3,031	57	8.1	100	12.2	53	8.3	104	12.8
40-50	176	2,904	51	8.1	125	16.4	49	8.8	127	17.4
50-60	111	2,735	17	6.9	94	19.5	15	6.2	96	22.3
60-70	27	2,432	3	10.0	24	29.0	3	15.3	24	28.8
70-80	3	2,670	1	0.0	2	24.0	1	0.0	2	30.0

sidered in determining vital capacity, as the degenerative changes and the changes in height and weight which appear in advancing years provide many reasons for such a decrease, but they are such variable factors that they are difficult to evaluate. This is more readily understood when one considers that the ravages of age appear at varying times, earlier in some persons than in others.

¹⁵ Lemon, W. S., and Moersch, H. J. Factors Influencing Vital Capacity, *Arch Int Med* 33:136-144 (Jan) 1924.

¹⁶ Arnett, J. H., and Kornblum, K. Vital Capacity: An Inquiry into Its Value as a Diagnostic Procedure, *Ann Clin Med* 3:255-274 (Oct) 1924.

Height—Hutchinson was the first to realize that the capacity of the lungs is dependent on certain bodily functions and to attempt to determine with which function it is most closely associated. He came to the conclusion that it is modified by four factors: height, weight, age and disease, height being the most important factor. He found that "for every inch of height from 5 to 6 feet, 8 additional cubic inches of air at 60 degrees are given out by forced expiration." The length of the trunk, the size of the chest as determined by plaster casts, the absolute capacity of the chest, and the depth of the thorax were found to have but little effect on the vital capacity. It has been stated by many observers that height bears a relationship to vital capacity, and there are many formulas for the estimation of the normal vital capacity from the height. Among

TABLE 4—*Variation in Vital Capacity According to Height*

Height Cm	Number		Average Vital Capacity, Cc	
	Males	Females	Males	Females
140-145	2	4	3,910	2,748
145-150		32		2,521
150-155	1	85	3,798	2,700
155-160	11	181	3,708	2,786
160-165	57	166	3,801	3,030
165-170	92	84	4,170	3,245
170-175	121	19	4,589	3,180
175-180	97	8	4,712	3,533
180-185	35		5,121	
185-190	2		6,041	
190-195	1		5,735	

TABLE 5—*Variation in Vital Capacity According to Height (Pratt)*

Height, Cm	Average Vital Capacity, Cc
150-155	2,900
155-160	3,150
160-165	3,400
165-170	3,725
170-175	3,950
175-180	4,300

the more common methods may be mentioned that of Peabody and Wentworth of dividing the males and females into three groups on the basis of height. Myers¹⁷ introduced the use of an arbitrary numeral along with height for estimating the vital capacity, and West¹⁸ used the same method. That such a relationship does exist may be seen from Table 4. It is interesting to compare the variations in height obtained in the present series with those obtained by Hutchinson eighty years ago (Table 5).

17 Myers, J. A. Studies on the Respiratory Organs in Health and Disease, II, A Study of the Vital Capacity and Physical Fitness of Nurses, *Journal-Lancet* 41 252-257 (May 1) 1921.

18 West, H. F. Clinical Studies on the Respiration, VI, A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, *Arch Int Med* 25 306-316 (March) 1920.

It can readily be seen in Tables 4 and 5 that there is a progressive increase in vital capacity with increase in height which, however, is not so marked in females as in males. The difference between the vital capacities at heights of 150 cm and 180 cm in Hutchinson's records was 1,150, and in the present series 1,004 c c, which shows fairly close agreement for such a large group. The difference in vital capacities for the same height in Hutchinson's series and mine is more apparent than real, and can be accounted for by Hutchinson's reduction of all his readings to an atmospheric temperature of 60 degrees. This reduction to a uniform temperature was not made in my series.

Weight—Weight, a factor that plays such an important part in the routine consideration of disease and often furnishes the clinician with an index of the general condition of the patient, is likewise found to influence vital capacity to a certain extent. Hutchinson observed that weight exerts an influence on vital capacity, but not as much as height. He found that "vital capacity does seem to increase from 100 to 200 pounds, and that between 105 and 155 pounds it increases 164 c c per pound in weight, and from 155 to 200 pounds this increase is overpowered and there is a loss of 39.5 cu in or 648 c c." Hewlett and Jackson,¹⁹ from a study of 400 college students, concluded that the correlations of vital capacity with height and weight are approximately equal, but it is not as accurate a correlation of vital capacity with the two together. Dreyer³ felt that there was a closer correlation between weight and vital capacity than between height and vital capacity and presented mathematical proof of his contention. However, it must be said with regard to Dreyer's deductions that they were made on such a small group that their true value may be questioned. West, Myers, Peabody and Wentworth and Lemon and Moersch,²⁰ however, tend to agree with Hutchinson. The influence of weight on vital capacity as deduced from the present series is shown in Table 6, and it is discernible that there is not so close a relationship between weight and vital capacity as in Table 4 between height and vital capacity. Further, it may be noted that the increase is fairly uniform up to 150 pounds (68 kg), but from there on tends to remain stationary or to decrease slightly, which is in agreement with Hutchinson's earlier deductions (Table 5).

Surface Area—Surface area seems to bear a closer relationship to vital capacity than any other measurement of the body. However, the objection raised to the use of the formula based on surface area, devised by West, or the methods of Dreyer³ or Hewlett and Jackson is that the

19 Hewlett, A. W., and Jackson, N. R. The Vital Capacity in a Group of College Students, *Arch Int Med* 29 515-526 (April) 1922.

20 Lemon, W. S., and Moersch, H. J. Comparison of Constants for the Determination of Vital Capacity, *Arch Int Med* 33 118-127 (Jan) 1924.

calculation of the surface area is too complicated. This difficulty is easily overcome by the use of the chart constructed by Boothby and Sandiford for the determination of the surface area according to the DuBois formula (Fig 2)

With this chart, all that is necessary is to connect the height and weight on the respective outside lines by means of a straight line and

TABLE 6—*Variation in Vital Capacity According to Weight*

Weight, Kg	Number		Average Vital Capacity, C c	
	Males	Females	Males	Females
30-40		8		2,394
40-50	16	122	3,521	2,702
50-60	97	170	4,106	2,921
60-70	164	140	4,511	3,012
70-80	92	86	4,782	2,989
80-90	29	38	4,653	3,068
90-100	12	10	4,424	3,059
100 and up	7	7	4,412	2,792

TABLE 7—*Variation in Vital Capacity According to Surface Area*

Surface Area, Sq M	Number		Average Vital Capacity, C c	
	Males	Females	Males	Females
1.20-1.30		4		2,411
1.30-1.40		37		2,532
1.40-1.50	17	108	3,647	2,750
1.50-1.60	28	119	3,647	2,895
1.60-1.70	90	127	4,202	3,010
1.70-1.80	109	81	4,475	3,018
1.80-1.90	80	60	4,815	3,142
1.90-2.00	62	17	4,776	3,158
2.00 and up	28	11	4,718	3,023

TABLE 8—*Percentage Variation Between Vital Capacity Based on Surface Area and on Height (West's Formula)*

Method	Males			
	Number Above Calculated Normal	Average Percentage	Number Below Calculated Normal	Average Percentage
Surface area	235	11.6	182	13.4
Height	257	13.7	160	12.4
	Females			
Surface area	137	8.8	402	17.7
Height	176	8.9	407	16.7

read off the figures for surface area where it crosses the middle line. Table 7 shows the relationship of surface area to vital capacity, and it will be noted that vital capacity increases with surface area, and that as the effect or influence of obesity becomes apparent, the relationship digresses. That there is a rather close agreement between the relationships of surface area and height to vital capacity may be seen from Tables 7 and 8.

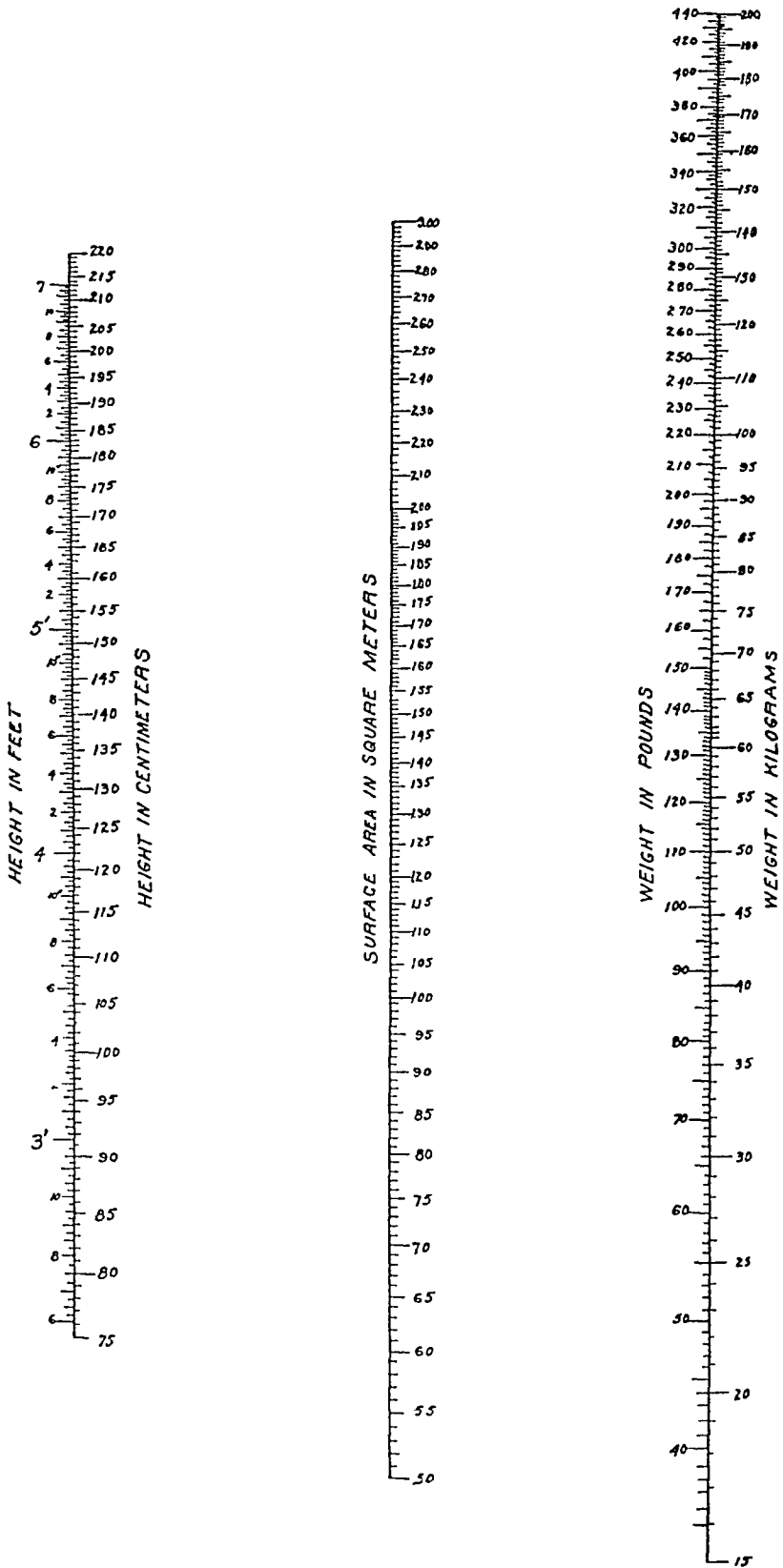


Fig 2—Surface area determinations (DuBois)

Variations in Vital Capacity Calculated from Height and from Surface Area—In calculating the normal vital capacity in the 1,000 patients studied, it was decided to see how great was the difference between the vital capacity as calculated first by body surface and by height according to West's formula surface area times 2.5 liters for men, and surface area times 2 liters for women, and height times 25 liters for men and 20 liters for women. If there was a close relationship, it would be more convenient to use the simpler method for routine purposes, especially as a chart for the calculation of surface area is not always available. The averages obtained from these two methods are presented in Table 9.

Organic Disease—It is well known that certain diseases may cause a decrease in vital capacity. Anything that interferes with the respiratory movements of the thorax, pleural and pulmonary changes, cardiac dis-

TABLE 9—Percentage Variation in Vital Capacity Above and Below the Calculated Normal in Various Diseases

Disease	Males				Females			
	Num- ber	Per Cent Above Normal	Num- ber	Per Cent Below Normal	Num- ber	Per Cent Above Normal	Num- ber	Per Cent Below Normal
Adenoma of thyroid	7	12.4	5	11.2	19	6.5	53	19.5
Appendicitis	28	14.0	12	9.2	20	10.0	38	15.5
Carcinoma of stomach	11	9.3	9	10.2	1	2.0	6	20.0
Carcinoma of bowel	17	11.4	9	15.0	2	5.0	4	19.8
Carcinoma of head and neck	2	21.0	6	8.7				
Carcinoma of breast and all other tumors of breast	1	10.0	1	14.0	13	10.0	28	16.9
Carcinoma of uterus					3	10.0	8	14.6
Carcinoma, miscellaneous	2	22.0	0	0.0	0	0.0	3	19.0
Cholecystitis	19	13.3	15	13.3	28	8.5	63	11.4
Duodenal ulcer	60	14.2	32	10.4	9	7.9	11	14.0
Gastric ulcer	14	11.1	7	9.6	14	11.1	7	9.6
Hernia	22	16.0	16	8.6	1	6.0	11	20.9
Abdominal tumor	3	5.6	1	3.7				
Pelvic and abdominal tumors					24	10.3	40	14.4
Kidney and bladder	20	13.5	30	12.7	2	3.0	11	16.3
Perineal and pelvic laceration					23	9.3	56	14.1

ease, hyperthyroidism, blood disturbances both chemical and cytologic, as well as prolonged infections, will cause a decrease in vital capacity.

Flexibility of Thorax—Peabody and Wentworth first called attention to the influence of flexibility of the thorax on vital capacity. The ability of the lungs to fill with air is dependent on the flexibility of the thoracic walls. Ossification of the costovertebral joints, cartilage, and so forth, may therefore affect vital capacity by decreasing the flexibility of the thoracic cage.

Intra-Abdominal Pressure—The effect of variations of intra-abdominal pressure on vital capacity is uncertain. It would seem probable that any condition in the abdomen that interfered with free movement of the diaphragm would influence it. Wittich, Myers and Jennings, and more recently Bell,²¹ found that pregnancy has little influence on vital capacity.

²¹ Bell, J. W. Personal communication to the author.

Equally important is the observation that Lewis²² made in animals in deep anesthesia, that variation in abdominal pressure plays no part in the production of respiratory curves. Patients with large abdominal tumors uncomplicated by other diseases do not show an abnormal decrease in vital capacity. Therefore, it would seem that increased intra-abdominal pressure per se without involvement of the diaphragm has very little influence on vital capacity.

Pleural and Pulmonary Changes—It is readily understood and easily demonstrated that anything that causes a decrease in the volume of the lung by retraction or displacement of the lung tissue will also cause a decrease in vital capacity, depending on the amount of tissue affected and the degree of interference with respiratory excursion or interference with the passage of air into other portions of the lungs. Hutchinson demonstrated this in 1846, in tuberculosis of the lungs. Since then Myers,²³ Hyge,²⁴ Shepard,²⁵ Dreyer and Burrell²⁶ have confirmed his observation and found that it varies fairly closely with the clinical and roentgenologic findings. Siebeck²⁷ believes that this decrease in vital capacity in tuberculosis is due to an increase in the volume of residual air, a decrease in the elasticity of the lung tissue and less forceful expiration. Myers,²⁸ Shepard, and Arnett and Kornblum found a rather marked characteristic drop in vital capacity in pneumonia, which is of especial diagnostic value in this condition. Myers,²⁸ Peabody and Wentworth found a decrease during attacks of bronchial asthma with a return to normal in persons in whom the condition was not associated with complications. Lemon and Moersch¹⁵ also observed a decrease with pleural effusions, pneumothorax, tumors of the chest and lung, pleural adhesions, cardiospasm, diverticula of the esophagus, bronchi-

22 Lewis, Thomas. Studies of the Relationship Between Respiration and Blood Pressure, *J Physiol* **37** 233-255, 1908

23 Myers, J A. Studies on the Respiratory Organs in Health and Disease, A Comparison of Lung Capacity Readings and Physical Signs in Pulmonary Tuberculosis, *Minnesota Med* **5** 233-237 (April) 1922

24 Hyge, T V. The Vital Capacity in the Tuberculous, *Hospitalstidende* **67** 341-350 (May 28) 1924

25 Shepard, W P. The Effect of Certain Past Diseases on Vital Capacity, *Arch Int Med* **33** 185-192 (Feb.) 1924

26 Dreyer, Georges, and Burrell, L S T. The Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, *Lancet* **1** 1212-1216 (June 5) 1920

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ectasis, emphysema, abscess of the lungs, and various conditions involving the respiratory apparatus

Hyperthyroidism—Recently McKinlay²⁹ and Rabinowitch⁶ have reported that a direct relationship exists between vital capacity and the severity of exophthalmic goiter and adenoma of the thyroid with hyperthyroidism, as expressed by the basal metabolic rate. On the other hand, Lemon and Moersch,³⁰ in a study of eighty-five patients with goiter, reported that no such relationship exists, the diagnosis in every instance having been confirmed by microscopic examination. Their conclusion was that one cannot accurately predict the decrease in vital capacity that will be associated with change in the basal metabolic rate.

So far as the decrease in vital capacity in hyperthyroidism is dependent on the degree of cardiac damage, it is evident from a study of a large series of goiter patients that no constant relationship exists between the basal metabolic rate and cardiac efficiency.

Diseases Not Related to the Respiratory Function—It is also of interest to know what influence the general diseases that require operative treatment have on vital capacity, for if the disease itself does not influence vital capacity we have much more reason to employ it as a routine in the examination of patients undergoing operation, to detect a large group of pulmonary and cardiac diseases which might pass unnoticed and thereby increase the operative mortality. In Table 9 is a list of the diseases manifested by the patients examined in the present study and the percentage variations in vital capacity from the normal. The group showing hyperthyroidism and cardiac and gross pulmonary disease are excluded in the classification for reasons already mentioned (Table 9).

It may be readily seen that the diseases named influence vital capacity very little. It should be stated that in many cases a multiplicity of diseases existed in the same patient although the chief complaint is listed in each instance, so that even multiple disease not involving the organs of external respiration does not cause a decrease in vital capacity. Patients having twenty-eight different types of disease also were examined, but in none did there appear to be a definite relationship between the disease and vital capacity. It may therefore be seen that determinations of vital capacity are of particular importance in routine examination of operative cases in which the patient has not had the benefit of a thorough medical examination, as it gives a fairly accurate index of the efficiency of the organs of external respiration.

29 McKinlay, C. A. The Vital Capacity of the Lungs and Its Significance in Hyperthyroidism, *Arch Int Med* **34** 168-176 (Aug.) 1924.

30 Lemon, W. S., and Moersch, H. J. Basal Metabolism and Vital Capacity, *Arch Int Med* **33** 130-135 (Jan.) 1924.

COMMENT

While many and diversified conditions, often of a baffling nature, require interpretation to obtain an accurate conception of the vital capacity of a subject, still the use of the spirometer fulfills a definite requirement in clinical medicine. While it may be truthfully said that determinations of vital capacity will not permit of a diagnosis without further data, when used as an adjunct to other clinical findings they may be of considerable importance. They are especially useful in following the course of cardiac and pulmonary disease. The greatest value of the spirometer lies in its ability to detect any disturbance of external respiration. Diseases that do not affect the cardiorespiratory functions have very little or no influence on vital capacity. This fact alone makes the spirometer of great value in the routine examination of patients or any large group of persons undergoing examination for physical fitness. While it will never be substituted for a thorough clinical and physical examination, still when this is not feasible or possible, it is a great aid in attracting the attention of the examiner to the possible presence of one of a large group of gross pulmonary or cardiac diseases. While in many instances a low vital capacity may exist without any demonstrable organic cause, in a large percentage organic disturbance involving the cardiorespiratory system may be demonstrated.

Clinicians and surgeons often tend to get out of touch with the patient's progress and often greatly overestimate his vitality. In long drawn out disease affecting the heart and lungs, frequent determinations of vital capacity will help to foretell the course of the disease. This is especially true when edema is present. When the patient is put to bed, the sudden disappearance of the edema may prompt a feeling that there has been a marked improvement. By the use of the spirometer it may be demonstrated in many instances that the disappearance of the edema is due to a shifting of fluid rather than to its actual absorption and excretion.

In the foregoing observations it has been my aim to point out the various factors that influence vital capacity and to show that diseases not involving respiration have no influence on vital capacity. Finally, through an accurate understanding of these influences, it has been my aim to demonstrate that if these influences are accurately understood, studies of vital capacity are of distinct clinical value.

CONCLUSIONS

1. Determinations of the vital capacity of the lungs should not be regarded as a diagnostic measure in itself, but rather as an aid to diagnosis, just as the use of the thermometer and sphygmomanometer are aids.

2 Various extraneous factors that influence vital capacity are posture, size, time elapsed since last meal, and psychic disturbances

3 Determinations of vital capacity are most accurate when calculated on the basis of surface area and height

4 The relationships of surface area and height to vital capacity are so similar that for most practical purposes the standard based on height alone will prove satisfactory

5 The vital capacity calculated on surface area tends to give higher values than that calculated on height alone

6 No formula in itself has proved satisfactory in all cases, as normals may give readings below 85 per cent of their calculated vital capacity. Therefore, it is not correct to regard every reading of more than 15 per cent below normal as pathologic

7 The same relationships tend to hold true in children as in adults

8 Physical fitness, sex, age, height, weight and surface area influence vital capacity

9 The number of pregnancies in a woman does not seem to influence vital capacity, the same being true of miscarriages

10 Anything that interferes with or influences the normal functions and activity of the lungs has a direct bearing on the vital capacity

11 Diseases not affecting or influencing the respiratory or cardiac system do not appreciably influence vital capacity

THE REFRACTOMETRIC AND VISCOSIMETRIC INDEXES OF CEREBROSPINAL FLUID *

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The determination of the refractive index of blood has been in use for several years owing to the work of Reiss,¹ Naegeli,² Rohrer³ and many others. It seemed to us worth while to determine the refractive index of cerebrospinal fluid. The literature reviewed by us revealed so far only two references to such determinations, the work of Polanyi⁴ and that of Molnar.⁵ It was our hope that the refractive index of cerebrospinal fluid in various conditions might yield some data that would be found useful for diagnosis, as has been the case in blood.¹ In order to do the work along the same lines as has been done on blood, it was deemed advisable to do viscosimetric readings together with refractometric determinations. It also was hoped that the combination of the two, the refractometric and the viscosimetric indexes, might throw light on the albumin-globulin ratio of cerebrospinal fluid.

GENERAL CONSIDERATION OF REFRACTOMETRY AND VISCOSIMETRY

Refractometry as a means of determining the amount of dissolved substances in fluids has been in use for about fifty years. Originally it was applied to the quantitative determination of sugar solutions. Later it was applied to the quantitative determination of protein in the blood. The proteins in the blood constitute 87 per cent of the dissolved serum substance. It was therefore believed and subsequently proved that except in extremely pathologic conditions, the blood salts, nitrogenous products and corpuscles can be disregarded in estimating the amount of dissolved proteins. The refractometric index in blood of normal persons has been found to vary between 1.34557 in infants under 1 month

* From the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1 Reiss, E. Die Refraktometrische Blutuntersuchung in ihre Ergebnisse für die Physiologie und Pathologie des Menschen, *Ergebn d inn Med u Kinderh* **10** 531-634, 1913.

2 Naegeli, O. Blutkrankheiten und Blutdiagnostik, Ed 3, 1924, p 39.

3 Rohrer, Fritz. Bestimmung des Mischungsverhältnisses von Albumen und Globulin in Blutserum, *Deutsch Arch f klin Med* **121** 140-221, 1916.

4 Polanyi. Beiträge zur Chemie der Hydrocephalusflüssigkeit, *Biochem Ztschr* **34** 205, 1911.

5 Molnar, A. L. Ueber die Refraktion der Menschlichen Lumbalflüssigkeit *Klin Wchnschr* **2** 790-791 (April 23) 1923.

of age, corresponding to 56 per cent. of protein, and 1.35110 in older children and adults, corresponding to 88 per cent of protein¹

In normal cerebrospinal fluid the amounts of protein, salts, nitrogenous substances and corpuscles are about equal in regard to their influence on the refractive index. As it is generally assumed that the proteins are the substances that are greatly increased in meningeal inflammations, we thought that the refractometer might serve to estimate this amount accurately.

The refractometer is an instrument that measures the deviation of light passing through fluids. Fluids refract transmitted light definitely and quantitatively according to the amount of dissolved substances. With the instrument we used, the Pulfrich dipping refractometer, determinations may be made with only 3 minims of fluid, a point of great importance in the study of cerebrospinal fluid. Readings are made from the scale of the instrument by means of a table and the readings are easily changed into the refractive index. Readings must be cor-

TABLE 1—*Effect of Time Element on Refractometry and Viscosimetry*

Case	Disease	Time of Examination	Refractometric Index	Viscosimetric Index
1	Meningococcus meningitis	Immediately	1.33574	1.11
		After 24 hours	1.33574	1.11
2	Meningococcus meningitis	Immediately	1.33533	1.11
		Centrifugated 10 minutes, then examined immediately	1.33531	1.10
		After 90 hours	1.33533	1.11

rected to 17.5 degrees C. For full description of the mechanism and use of the instrument, the reader is referred to the work of Reiss¹

The viscosimeter determines the viscosity of fluids. The fluid is sucked through one capillary tube while water is sucked through another tube of equal caliber. The reading is made with the tube through which water is sucked. The factors causing changes in viscosity, as in refractometry, are the dissolved substances. Correction must be made for the temperature to about 20 degrees C. The viscosity of the blood varies in normal persons from 1.43, corresponding to 5 per cent protein, to 1.9, corresponding to 9.5 per cent protein.

Allowing the fluid to stand several hours before examination apparently has no effect on the refractometric and viscosimetric indexes. Fluids from two patients with meningococcus meningitis which were allowed to stand for twenty-four and ninety hours, respectively, showed no change in either index at the end of that period (Table 1).

Centrifugating of the fluid immediately also produced no change in the indexes.

Bloody fluid, however, gives higher refractometric and viscosimetric indexes.

REFRACTOMETRIC INDEX

We examined 115 fluids obtained from ninety-three patients. These fluids were divided as follows. Sixty-six fluids were obtained from so-called normal patients, namely, patients who had no meningeal inflammation. We believe that one seldom obtains a real normal cerebrospinal fluid. The very fact that a fluid has to be withdrawn from the body indicates that there is some symptom leading to a suspicion of disturbances of the nervous system. We shall, therefore, designate this group of so-called normal cases as nonmeningitic. Sixteen specimens were taken from fourteen patients suspected to be syphilitic. Of these, three were found to be actively syphilitic and the rest had a negative Wassermann reaction, although they had a history of syphilitic symptoms or of previous syphilitic infection. Seven fluids were obtained from patients with tuberculous meningitis, fifteen fluids from three patients with meningococcus meningitis, and eleven fluids from seven patients with purulent meningitis other than meningococcal.

Nonmeningitic Fluid—In a series of miscellaneous cases, such as rickets and appendicitis, in which there was either no involvement of the nervous system, or in which there were nervous manifestations that later proved to be nonmeningitic and nonsyphilitic, excepting compression myelitis and one case of hydrocephalus, the refractometric readings ranged between 1.33472 and 1.33545, with an average of 1.33508 (Table 2). These may be further subdivided into the following:

In four cases of Little's disease, the reading ranged between 1.33472 and 1.33529, in ten cases of epilepsy, between 1.33493 and 1.33517, in two cases of mongolian idiocy and one case of imbecility, between 1.33500 and 1.33514, in two cases of encephalitis, the reading was 1.33509 and 1.33511, in three patients recovered from encephalitis, the reading ranged between 1.33498 and 1.33527, in nine cases of pneumonia and otitis media, between 1.33478 and 1.33521, in seven cases of hypertension, between 1.33500 and 1.33532, in three cases of brain and spinal cord tumor, between 1.33509 and 1.33523, and in one case of congenital heart disease, the reading was 1.33545.

Hydrocephalus and Compression Myelitis—In one case of ventricular fluid from a noncommunicating hydrocephalus, the reading was 1.33747, in two other cases, 1.33518 and 1.33511. In one case of compression myelitis, the reading was 1.33700. A comparison between ventricular and lumbar cerebrospinal fluid in one case showed a very slight difference in the reading.

Syphilitic Fluid—In three cases of active syphilis and eleven cases of latent or inactive syphilis, the refractometric readings varied, the lowest being 1.33513. The upper range was 1.33557, the average being 1.33525 (Table 3).

TABLE 2—*Refractometric and Viscosimetric Readings in Nonmeningitic Fluid*

Case	Disease	Age	Glob- ulin	Cells	Wasser- mann Reac- tion	Colloidal Gold Test	Refrac- to- metric Index	Viscosi- metric Index
1	Little's disease	7 yr	Neg	8	Neg	1111000000	1 33500	1 05
2	Little's disease	3 yr	Neg	26	Neg	0000000000	1 33487	1 05
3	Little's disease	17 mo	Neg	0	Neg		1 33472	1 09
4	Little's disease	12 mo	Neg	3	Neg	0001100000	1 33529	1 06
5	Epilepsy	47 yr	Neg	2	Neg	0011110000	1 33516	1 06
6	Epilepsy	11 yr	Neg		Neg	0000000000	1 33493	1 11
7	Epilepsy	6 yr	Neg	4	Neg	1222100000	1 33508	1 05
8	10/24/24 Epilepsy and idiocy	15 mo	Neg	12	Neg	0111100000	1 33509	1 05
	11/ 4/24		Neg		Neg	1110000000	1 33493	1 07
9	Epilepsy	3 yr	Neg	0	Neg	0000000000	1 33517	1 07
10	Epilepsy	36 yr	Neg	3	Neg	0222100000	1 33510	1 05
11	Jacksonian epilepsy	18 mo	Neg	10	Neg	0111000000	1 33499	1 06
12	2/29/25 Epilepsy and cocaine poisoning	19 yr	Pos	59	Neg	1222100000	1 33511	1 05
	3/3/25		Neg	0	Neg		1 33508	1 05
13	Epilepsy and chronic nephritis	49 yr	Neg	8	Neg	1223321000	1 33514	1 05
14	Epilepsy	21 yr	Neg	0	Neg	1244320000	1 33514	1 05
15	Epilepsy	8 yr	Neg	4	Neg	0000000000	1 33515	1 06
16	Mongolian idiocy	18 mo	Neg	6	Neg	0012100000	1 33500	1 05
17	Imbecility	2 yr	Neg	0	Neg	0000001100	1 33514	1 05
18	Encephalitis, active	45 yr	Neg	4	Neg	0011221000	1 33511	1 04
19	Encephalitis, active	15 yr	Neg	4	Neg	0111000000	1 33509	1 05
20	Encephalitis, recovered	13 yr	Neg	1	Neg	0000000000	1 33527	1 05
21	Encephalitis, recovered	5 yr	Neg	8	Neg		1 33498	1 05
22	Encephalitis, recovered	9 yr	Neg	7	Pos	0023320000	1 33502	1 05
23	Pneumonia and otitis media	2 yr	Neg	6	Neg	0000000000	1 33520	1 05
24	Pneumonia	6 yr	Neg	2	Neg	0133000000	1 33486	1 06
25	Pneumonia	11 yr	Neg	0	Neg		1 33497	1 08
26	Erysipelas	7 yr	Neg	0	Neg	0000000000	1 33509	1 05
27	Otitis media	16 mo	Neg	4	Neg	0000000000	1 33494	1 05
28	1/15/25 Otitis media and sinus thrombosis	12 yr	Neg	0	Neg	0000000000	1 33506	1 06
	1/21/25 Otitis media and peri carditis		Neg	83			1 33478	1 05
	1/22/25		Neg	10			1 33509	1 05
29	Otitis media	2 yr	Neg	8	Neg	0000000000	1 33481	1 05
30	Otitis media and acute nephritis	13 yr	Neg	0	Neg	0011100000	1 33521	0 05
31	Sepsis	19 yr	Neg	0	Neg	0002110000	1 33490	1 05
32	Hypertension and angiospasm	47 yr	Neg	8	Neg	0012320000	1 33504	1 05
33	Hypertension and diabetes mellitus	52 yr	Neg	0	Neg	0000000000	1 33522	1 05
34	Hypertension	50 yr	Neg	2	Neg	0000000000	1 33513	1 05
35	Hypertension	34 yr	Neg	4	Neg	0000000000	1 33500	1 05
36	Hypertension	48 yr	Neg	0	Neg	0000000000	1 33502	1 10
37	Hypertension and cerebral thrombosis	60 yr	Neg	12	Neg	0000000000	1 33509	1 05
38	Hypertension and cerebral hemorrhage	54 yr	Neg	7	Neg	0000000000	1 33532	1 05
39	Hysteria	10 yr	Neg	4	Neg	0000000000	1 33517	1 05
40	Senility	59 yr	Neg	9	Neg	0012220000	1 33528	1 07
41	Hyperthyroidism	36 yr	Neg	0	Neg	0011110000	1 33501	1 07
42	Chronic nephritis	19 yr	Neg	4	Neg		1 33510	1 05
43	Senility	37 yr	Neg	2	Neg	0000000000	1 33519	1 04
44	Aortitis	65 yr	Pos	80	Neg	0000000000	1 33508	1 06
45	Myocarditis	50 yr	Pos	14	Neg	0033200000	1 33496	1 05
46	Marie's disease	59 yr	Neg	2	Neg	0000000000	1 33509	1 05
47	Rachitis	15 mo	Neg	6	Neg	0000000000	1 33492	1 05
48	Infected tonsils	32 yr	Neg	0	Neg	0111000000	1 33513	1 05
49	Appendicitis	26 yr	Neg	1	Neg	0111100000	1 33500	1 05
50	Duodenal ulcer	50 yr	Neg	2	Neg	0000000000	1 33517	1 05
51	Duodenal ulcer	38 yr	Neg	0	Neg	0000000000	1 33514	1 05
52	Neurasthenia	20 yr	Neg	12	Neg	0011100000	1 33500	1 05
53	Congenital heart disease	3 mo	Neg	4	Neg		1 33545	1 09
54	Occupational paresis	39 yr	Neg	0	Neg	0000000000	1 33501	1 05
55	Multiple sclerosis	40 yr	Neg	0	Neg	0012100000	1 33501	1 05
56	Brain tumor	3 mo	Neg	4	Neg		1 33523	1 05
57	Brain tumor	40 yr	Neg	12	Neg	1111100000	1 33509	1 06
58	Spinal cord tumor	44 yr	Pos	120	Neg	0011100000	1 33511	1 05
59	Compression myelitis and carcinoma of the breast	55 yr	4+	6	Neg	1110000000	1 33700	1 11
60	Hydrocephalus and encephalitis, recovered	13 mo	Neg	0	Neg	0000000000	1 33518	1 09
61	Hydrocephalus and mongolian idiocy	12 mo	Neg	0	Neg	0000000000	1 33511	1 05
62	Hydrocephalus, congenital	3 mo	4+				1 33747	1 20

TABLE 3—*Refractometric and Viscosimetric Readings in Syphilitic Fluid*

Case	Disease	Age	Glob- ulin	Cells	Wasser- mann Reac- tion	Colloidal Gold Test	Refrac- to- metric Index	Viscosi- metric Index
		A	Active					
1	Tabes dorsalis	32 yr	4+	20	4+	0014420000	1 33524	1 04
2	Involvement of central nerv- ous system	49 yr	1+	222	4+	0244444431	1 33521	1 05
3	Involvement of central nerv- ous system	28 yr	4+	240	4+	0022332100	1 33529	1 06
		B	Inactive					
4	Neurovascular	27 yr	2+				1 33535	1 07
5	Inactive	30 yr	Neg	0	Neg	0012221000	1 33514	1 06
6	Inactive	37 yr	Neg	0	Neg	0000000000	1 33513	1 05
7	Inactive	28 yr	1+	12	Neg	0000034300	1 33526	1 05
8	Central nervous system	18 yr						
	(a) 1/16/25		4+	40	Neg	1123332100	1 33520	1 07
	(b) 1/17/25		4+	27			1 33552	1 07
	(c) 1/25/25		4+	25			1 33529	1 06
9	General paresis	48 yr	4+	55	Neg	1133333100	1 33524	1 05
10	Central nervous system	61 yr	Neg	0	Neg	0012210000	1 33517	1 05
11	General paresis	62 yr	Neg	0	Neg	0001110000	1 33557	1 06
12	Vascular, inactive	55 yr	Neg	9	Neg	0012210000	1 33515	1 05
13	Inactive	44 yr	Neg	0	Neg	0011100000	1 33513	1 05
14	Meningitic	11 yr	Neg	18	Neg	0023321000	1 33513	1 05

TABLE 4—*Refractometric and Viscosimetric Readings in Meningitic Fluid*

Case	Disease	Age	Glob- ulin	Cells	Wasser- mann Reac- tion	Colloidal Gold Test	Refrac- to- metric Index	Viscosi- metric Index
1	Tuberculous meningitis	7 yr		140	Neg	0001333200	1 33490	1 05
2	Tuberculous meningitis	18 yr	1+	165	Neg	0000233100	1 33616	1 15
3	Tuberculous meningitis	43 yr	1+	110	Neg		1 33570	1 18
4	Tuberculous meningitis	2 yr	2+	194	Neg	0011233210	1 33523	1 09
5	Tuberculous meningitis	5 mo	4+	178	Neg	0122344110	1 33552	1 06
6	Tuberculous meningitis	5 yr		90	Neg	0002330000	1 33473	1 05
7	Tuberculous meningitis	18 mo		25	Neg		1 33487	1 05
8	Meningococcus meningitis	25 mo						
	(a) 9/19/24 Before serum		4+	10,000	Neg	0001123443	1 33525	1 14
	(b) 9/20/24 After 20 cc of serum		1+				1 33540	1 13
	(c) 9/21/24 After 60 cc of serum		1+				1 33536	1 11
	(d) 9/21/24 After 80 cc of serum		1+				1 33555	1 10
	(e) 9/22/24 After 100 cc of serum		1+				1 33521	1 12
	(f) 9/23/24 After 120 cc of serum		1+				1 33574	1 11
	(g) 9/24/24 After 140 cc of serum		1+	2,000			1 33644	1 12
	(h) 9/29/24 Improved						1 33591	1 08
9	10/5/24 Meningococcus menin- gitis	5 mo	4+	4,190	Neg	0001123454	1 33543	1 14
	10/6/24 After 15 cc of serum (prognosis grave)		4+				1 33524	1 07
10	Meningococcus meningitis		4+	4,900				
	(a) 10/10/24 Before serum		4+		Neg	0000255442	1 33571	1 13
	(b) 10/11/24 After 80 cc of serum		4+	1,944			1 33510	1 10
	(c) 10/12/24 After 110 cc of serum		4+	3,798			1 33500	1 10
	(d) 10/13/24 After 140 cc of serum		4+	2,574			1 33487	1 10
	(e) 10/13/25 After 170 cc of serum, condition poor		4+	3,024			1 33533	1 11
11	Streptococcus meningitis	9 yr	Neg		Neg		1 33517	1 06
12	Streptococcus meningitis	4 yr			Neg	1111234444	1 33504	1 05
	(a) 1/6/25		Neg	7	Neg			
	(b) 1/21/25		Neg	12			1 33497	1 05
	(c) 2/1/25					0000123433	1 33525	1 05
13	Streptococcus meningitis	55 yr	4+	4,752	Neg	0000034444	1 33593	1 08
14	Streptococcus meningitis (Postmortem fluid)	8 mo					1 33924	1 31
15	Streptococcus meningitis	4 mo						
	(a) 3/22/25 Ventricular fluid		4+	100			1 33673	1 13
	(b) 3/23/25 Ventricular fluid		4+	200			1 33703	1 14
	(c) 3/25/25 Ventricular fluid						1 33704	1 13
16	Pneumococcus meningitis	18 mo	4+	2,578	Neg	0013333332	1 33639	1 09
17	Pneumococcus meningitis	2 mo	4+	400	Neg	0000144444	1 33518	1 08

Meningitic Fluid—In seven cases of tuberculous meningitis, the reading ranged from 1 33473 to 1 33616, with an average reading of 1 33530. In fifteen fluids from three patients with meningococcus meningitis, the readings varied between 1 33487 and 1 33644, with an average reading of 1 33544, most fluids having a refractometric reading higher than the usual figures for nonmeningitic fluid. In eleven fluids from seven patients with other purulent meningitis, the reading varied between 1 33497 and 1 33924, with an average of 1 33618, most fluids having a high refractometric reading (Table 4).

The refractometric readings in the nonmeningitic and the non-syphilitic cases, with the exception of one case of hydrocephalus and one case of compression myelitis, varied between 1 33472 and 1 33545. This differs only slightly from Molnar's figures, as in his series of "normal cases" the readings varied between 1 33486 and 1 33517. It also differs only very slightly from Polanyi's figure, which was 1 33554 at 20 degrees C. The high reading in our case of hydrocephalus agrees with the reading of Molnar, whose figures in one case of hydrocephalus was 1 3386, even higher than in our case. Our readings in cases of brain tumors do not justify the assumption of Molnar that the refractive index may be of diagnostic value in cases of brain tumor. In our three cases of brain and spinal cord tumors our readings were low.

VISCOSIMETRIC READINGS

In sixty-six nonmeningitic and nonsyphilitic fluids, the viscosimetric reading in sixty-two cases ranged between 1 04 and 1 09, with an average of 1 05. One case of hypertension, one of epilepsy and one of compression myelitis due to carcinoma gave a reading of 1 10 or over. The case of congenital hydrocephalus gave a reading of 1 20. In syphilitic fluids, both active and inactive, the viscosity varied between 1 04 and 1 07, with an average of 1 05. In the seven cases of tuberculous meningitis the viscosity varied between 1 05 and 1 18, with an average reading of 1 09. The fifteen determinations of fluids from cases of meningococcus meningitis ranged in their viscosimetric readings between 1 07 and 1 14, with an average reading of 1 11. It should be remembered, however, that some of the fluids in this group of cases were drawn after antimeningococcus serum had been given. The viscosity in other suppurative meningitides varied between 1 05 and 1 31, with an average of 1 11.

There is very little data in the literature on the viscosity of the cerebrospinal fluid. Polanyi found it to vary between 1 020 and 1 027.

at 38 degrees C, using water as the standard of 1. In our previous work,⁶ we found the viscosity between 1.0424 and 1.0489 compared to water. We used the Ostwald apparatus for our first series of determinations. In the present series, as stated above, we used the Hess instrument.

SUMMARY

1 Sixty-six specimens of cerebrospinal fluid obtained from non-meningitic and nonsyphilitic patients gave a refractometric reading of 1.33472 to 1.33545, with an average of 1.33508. There were two exceptions to this rule, namely, one case of hydrocephalus and one case of compression myelitis, both of which gave an unusually high reading.

2 In fluid from active and inactive syphilis, the refractometric reading varied between 1.33513 and 1.33557, with an average of 1.33525.

3 Seven cases of tuberculous meningitis gave refractometric readings varying between 1.33475 and 1.33616, with an average of 1.33530. In fifteen fluids from three cases of meningococcus meningitis, the readings varied between 1.33487 and 1.33644, with an average reading of 1.33544. Eleven fluids from seven cases of other forms of purulent meningitis varied between 1.33497 and 1.33924, with an average reading of 1.33618.

4 The viscosity in sixty-two out of sixty-six fluids from nonmeningitic cases ranged between 1.04 and 1.09, with an average reading of 1.05. The viscosity in seven fluids from cases of tuberculous meningitis varied between 1.05 and 1.18, with an average reading of 1.09. The viscosity in fifteen fluids of meningococcus meningitis varied between 1.07 and 1.14, with an average of 1.11. The viscosity in fluids from other forms of suppurative meningitis also averaged 1.11.

5 The refractometer and viscosimeter may serve as a means of determining a marked increase in the protein of cerebrospinal fluid, but cannot be used for the determination of a slight increase in the protein.

6 A marked increase in the refractometric and viscosimetric readings speaks for a pathologic process of the nervous system, such as meningitis, obstructive hydrocephalus or compression myelitis. Normal refractometric and viscosimetric readings do not exclude a pathologic process of the nervous system.

7 Refractometric and viscosimetric readings do not change with the age of the fluid.

8 The cerebrospinal fluid must be free from blood for refractometric and viscosimetric determinations.

⁶ Levinson, A. *Cerebrospinal Fluid in Health and in Disease*, Ed 2, St Louis, C. V. Mosby Company, 1923.

Book Reviews

DISEASES OF THE BRONCHI, LUNGS AND PLEURA By FREDERICK T. LORD, M.D., Visiting Physician, Massachusetts General Hospital, Instructor in Medicine, Harvard Medical School. Second Edition, Thoroughly Revised, with the Addition of Chapter on Pulmonary Tuberculosis. Pp. 776, with 110 illustrations. Price, \$8.00. Philadelphia: Lea & Febiger, 1925.

The first edition of Lord's book on diseases of the bronchi, lungs and pleura, which appeared in 1915, was favorably received by the profession. Many expressed regret that a consideration of tuberculosis was omitted. In the present edition more than 100 pages are devoted to a comprehensive discussion of the subject. In addition to this valuable feature, the book has been revised and considerable new material has been added. Among the most important additions are those concerning atelectasis, the etiology and treatment of bronchial asthma, the newer conceptions of the resolution and recovery from lobar pneumonia, streptococcus bronchopneumonia and empyema, bronchoscopy, increase in the scope of thoracic surgery, the roentgen ray in diagnosis and the treatment of acute empyema by closed drainage.

In this edition the same high standards are maintained and the profession is given the benefit of fifteen years' additional experience by one who has made an extensive study of the field. The book will therefore serve as a valuable reference for the student and teacher and a trustworthy guide for the practitioner.

TRAITEMENT DU DIABETE By PEDRO ESCUDERO, Professeur de clinique médicale à l'Université de Buenos Ayres. Paris: Norbert Maloine, 1925.

A reviewer, pondering over modern thought and modern publications on diabetes, encounters difficulty in harmonizing the many divergent views of practice. High fats and low fats are advocated, protein is used and abused, the safe fatty acid-glucose ratio is variously estimated, and one wonders over the fact that most patients who are adequately treated get along equally well under so many different regimens. The reason must be, of course, that each system has certain fundamental similarities in principle, even though the existing confusion hides the parallelism.

To such a reviewer this book from a South American colleague comes as a real pleasure. The basis of diabetic treatment has always been the same—the dietetic regimen. Insulin has not modified or simplified this treatment, but has rendered it really efficacious. No extreme ideas of dietotherapy are accepted, the perversion of metabolism is not systematic, each diabetic patient must have his own regimen. "Hyponutrition" (undernourishment) is used in the beginning of treatment, and starvation as a heroic method in the control of acidosis. But to establish "le régime définitif," preconceived preference does not prevent the employment of protein, fat and carbohydrates entirely as dictated by the needs and capacity of the individual patient. Patients with severe diabetes require insulin. The physician wastes his time on patients who will not, or cannot, cooperate.

These few paraphrases from the preface indicate the character of the book. Clinical details are many, discussion of various schemes of treatment full. Excellent food tables and diet lists are found at the end, insulin is thoroughly and practically discussed in an appendix of thirty-two pages. We believe that this volume is not surpassed by any French book on the subject.

MEDICINE AN HISTORICAL OUTLINE By M G SEELIG, M D, Professor of Clinical Surgery in the Washington University School of Medicine, Baltimore
Baltimore Williams & Wilkins Co, 1925

In a delightful foreword, Dr Fielding H Garrison speaks of the device of lecturing as a dubious one in any subject, but adds with truth that the lectures under review are "fresh, informing, brief and to the point" Dr Seelig has done a useful piece of work in preparing an outline of medical history, which no doubt was followed with enthusiasm by his hearers It is fortunate that the lectures have appeared in book form and can be read in a few hours and referred to at will

Dr Seelig's book is an outline, but it also is a sound guide to the beginner in medical study or to the intelligent layman who wishes to gain a rapid view of the subject The informed, even the specialist in medical history, can read it with pleasure and profit, if only to get the author's method and point of view

The work begins with the evidences of superstition and folklore in medicine, with pithy comments on many details, and early discloses a broad and accurate knowledge of general history Egyptian, Babylonian and Jewish medicine are adequately touched on Greek and Roman medicine are described in a few pages After brief consideration of the Middle Ages, the narrative becomes more detailed and follows through the centuries This division of time is convenient and will be found, especially by the beginner, to have distinct advantages

It is easy to criticize details in any work so condensed as this, but there is nothing serious to comment on here Dr Seelig is in good company in his treatment of Paracelsus, yet the skeptic may think that he has overidealized that strange character Perhaps the account of Paré will be more generally acceptable, many will think that John Hunter has been dismissed too soon A few questionable or inaccurate statements may be ascribed to hasty preparation It seems erroneous to speak of the popularization of the clinical thermometer in the eighteenth century Parry's description of exophthalmic goiter in 1786 exerted no influence until many years later Some chronologic dislocations occur, as the consideration of Bichat before Morgagni The proofreading could have been improved The faults, however, are trifling in comparison with the general accuracy, the fulness, and the terse and engaging style of the author It is to be hoped that the volume will have wide use among students in premedical and medical years Public libraries cannot do without it

THE RELATION OF ALBUMINURIA TO PROTEIN REQUIREMENT IN NEPHRITIS

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WITH THE ASSISTANCE OF

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The proper composition of nephritic diets has been a continuous source of controversy. Since it was first demonstrated that certain patients with renal disease retained nitrogenous waste products, it has become general practice to restrict the protein of the diet in all cases of nephritis. This tendency received a further impetus from the misconception that urea and other protein metabolites that accumulated in the blood of persons with impairment of kidney function were themselves responsible for some of the symptoms of uremia. The general burden of evidence goes to prove that this is not the case and that urea concentrations quite as great as those encountered in the blood of some patients with nephritis are incapable of producing anything resembling the uremic syndrome. An extended investigation of the nonprotein nitrogenous constituents of the blood in nephritis has also revealed the fact that retention of these waste products may be, and usually is, lacking or an insignificant feature in certain types of nephritis, and notably in those chronic or subacute types which are characterized especially by edema which is not due to cardiac decompensation, the parenchymatous nephritis of older terminologies, the nephroses and the nephrotic forms of glomerulonephritis of Volhard and Fahr.¹

The failure to find a justification for the indiscriminate use of low protein diets in the results of chemical analysis of blood has not convinced the advocates of this therapeutic procedure of its error. The theory that the end products of protein catabolism are renal irritants or

¹ From the department of internal medicine of Yale University School of Medicine and the medical service of the New Haven Hospital.

1 Volhard, Franz. Die doppelseitigen hamatogenen Nierenkrankheiten, 1918. Volhard, Franz, and Fahr, T. Die Brightsche Nierenkrankheiten, Berlin, 1914. Fahr, T. Virchows Arch f path Anat **239** 32, 1922.

that by relieving the kidney of the necessity of excreting these products the organ is rested has furnished new pretexts for its continuation. Some support for the idea that proteins are deleterious has been given by Newburgh,² who has produced nephritis in rabbits by the administration of diets containing excessive amounts of protein. The fact that the administration of excessive protein to a vegetarian animal results in the development of nephritis is no good evidence that ordinary amounts of protein will have a similar effect on an omnivorous animal.

If protein waste products are injurious to the kidney or strain it, and this is by no means established, the rational procedure is to give not an excessively low protein diet, but a diet that will reduce the nitrogen metabolism to a minimum, the two are not necessarily synonymous. Even this alone is not sufficient. Complete protein starvation with the administration of large amounts of carbohydrate and fat will effect an extreme reduction of nitrogen metabolism and has been employed as a temporary expedient in the treatment of uremia. It is not, however, a procedure that can be continued indefinitely, because protein wastage is itself attended with serious results. Nephritis is a chronic disease and treatment must, therefore, be so regulated that it can be continued for an indefinite period. It is essential that reduction of protein be controlled to insure the patient against the effects of protein starvation. In other words a negative nitrogen balance must be avoided. This is possible only if a sufficient minimum of protein and an adequate amount of carbohydrate are given.

The literature is strangely lacking in studies of nitrogen metabolism directed to the determination of the actual protein and caloric requirements of nephritic patients. Mosenthal and Richards³ and others have shown that under certain conditions there may be an increased destruction of protein in the body. They also have pointed out that a negative nitrogen balance is often associated with a rising blood nonprotein nitrogen, while, when the nitrogen output diminishes, the blood nonprotein nitrogen also may fall. In these cases the alterations of blood chemistry are as much due to changes of metabolism as they are to renal impermeability and the effect of these metabolic changes cannot safely be ignored in the regulation of diet.

Another factor also has been largely neglected, albuminuria. Albuminuria represents the excretion of preformed protein which has, presumably, played no part in the metabolic processes of the body and served no useful purpose in the economy of the organism. It is generally believed that this protein is derived from the serum albumin to

2 Newburgh, L. H. The Production of Bright's Disease by Feeding High Protein Diets, *Arch Int Med* **24** 359 (Oct.) 1919.

3 Mosenthal, H. O., and Richards, A. C. The Interpretation of a Positive Nitrogen Balance in Nephritis, *Arch Int Med* **17** 329 (Feb.) 1916.

which, under certain circumstances, the kidneys become permeable. This loss of serum albumin may play an important part in the production of the low proteins of those forms of nephritis in which albuminuria is an especially striking symptom, the parenchymatous nephritides, the nephroses or the nephrotic types of glomerulonephritis. Some disturbance of the mechanism for the regeneration of the serum proteins also may be active. There is no reason for believing that the nitrogen of urine albumin plays any rôle in the normal protein metabolism of the body nor is there any convincing evidence that the metabolism of patients with albuminuria is especially low. It is fair to assume, then, that such patients will excrete the usual amount of nonprotein nitrogen and in addition an amount equivalent to the proteinuria.

It is reasonably certain that the diet can be so adjusted as to provide for the nonprotein nitrogen loss. How much excess protein will be required to replace the albumin excreted is less certain. In fact it is not possible to say *a priori* whether it can be replaced at all. If an ordinary person is fed an excess of protein the surplus accumulates in the body only to a limited extent and almost immediately the nitrogen excretion rises to the level of the nitrogen intake and equilibrium is established. In this case all the nitrogen is broken down and excreted in the form of urea and the other common nitrogenous end products.

Epstein,⁴ realizing the part that protein loss probably plays in these cases and believing that the low concentration of plasma proteins was itself partly responsible for the appearance of edema, long since advocated high protein diets. Clinical observation convinced him that such diets were distinctly beneficial. Others have been less favorably impressed by Epstein's diets. The opinion of Linder, Lundsgaard and Van Slyke⁵ is representative of the conclusions that have been reached by those who have given the subject serious study and thought. These authors believe that diets should contain an adequate but not excessive amount of protein. Unfortunately we are quite ignorant of what an adequate amount of protein may be.

Recent work of McLean⁶ and Wordley⁷ also has an interesting bearing on the problem. These authors believe that the beneficial effect of high proteins is largely due to the diuretic effect of the increased

4 Epstein, A. A. Concerning the Causation of Edema in Chronic Parenchymatous Nephritis, Method for Its Alleviation, *Am J M Sc* **154** 638 (Nov) 1917

5 Linder, G. C., Lundsgaard, Christen, and Van Slyke, D. D. The Concentration of the Plasma Proteins in Nephritis, *J Exper Med* **39** 887 (June) 1924

6 McLean, Hugh. Modern Methods in the Diagnosis and Treatment of Renal Disease, London, 1924

7 Wordley, E. The Effect of High Protein Diet on Albuminuria and Blood Urea in Cases of Nephritis, *Quart J Med* **14** 88 (Oct) 1920

urea formed from them. They advocate the administration of urea itself. Although this will seem to many dangerously unorthodox, the clinical results obtained by them with doses ranging from 20 to 45 gm of urea a day in cases of nephritis with edema, but without any tendency to nitrogen retention, are worthy of consideration.

The work presented here was undertaken in an attempt to learn something of the nitrogen metabolism in nephritis, to establish more definitely the nitrogen requirements of the disease, to find out whether, and how, protein lost as albumin could be replaced, and to study the effect of feeding on the level of the plasma proteins, the clinical aspects of the disease and the chemical composition of the blood.

This paper deals with a study of the protein metabolism in the types of nephritis characterized especially by the occurrence of edema (which is not referable to cardiac decompensation), profuse albuminuria and reduction of the plasma proteins, with little tendency to the development of nitrogen retention, hypertension and its complications, retinitis or uremia except as terminal symptoms. This is the type of nephritis that has long been known as chronic or subacute parenchymatous, and it includes Volhard and Fahr's nephrosis as well as their nephrotic form of glomerulonephritis. The failure to distinguish between these two diseases does not imply that the authors are convinced that such a distinction is unwarranted. On this subject they are entirely open minded. For reasons that will appear, however, they do feel that the distinction is clinically difficult or impracticable in the majority of instances.

Among adults, to whom this study is almost entirely confined, clear cut examples of this disease are comparatively rare. The investigations do not, therefore, include a large number of cases. A variable amount of work was done on each patient, depending largely on the character of the individual. As these studies were carried out in the general medical wards, in large part while the metabolism department was still in process of development, much of the work done had to be discarded because of faulty collections of urine or the administration of improper diets. All data concerning the accuracy of which there was room for reasonable doubt have been discarded. The amount that remains represents a pitifully small fraction of the work that was done but is, we believe, reliable in all essential respects.

PROCEDURE

Diets were prepared in the special diet kitchen of the hospital. Protein and calories were estimated from the usual Atwater and Bryant⁸ tables. Chloride was calculated by means of the analyses of Sherman.⁹ In all probability the

⁸ Atwater, W. O., and Bryant, A. P. Chemical Composition of American Food Materials, Bull. U. S. Dept. Agriculture, No. 28, 1906.

⁹ Sherman, H. C. Chemistry of Food and Nutrition, Ed. 2, 1924, New York: Macmillan Company, p. 421.

chlorid values given are minimal. Occasionally it proved necessary to use canned vegetables. Whenever possible these were washed once and the water discarded. Although this probably failed to remove all the salt, further washing seemed inadvisable. Fluids were carefully measured and the amounts administered were recorded when they were given by the nurse in charge of the case. Urine specimens were collected in bottles that contained a small amount of toluene and sent to the hospital laboratory of the department of internal medicine, where they were accurately measured and analyzed. The cooperation and interest of the patient was enlisted in the recording of fluids and the collection of urine. Patients were weighed at the same time every day.

Total urinary nitrogen was estimated by the usual Kjeldahl procedure. For the determination of nonprotein nitrogen a fraction of the urine was treated with an equal amount of 10 per cent trichloroacetic acid solution. The precipitated protein was filtered off and an aliquot portion of the filtrate was then analyzed for nitrogen. Salt was estimated by the usual Volhard-Harvey titration.

Blood was withdrawn from an artery or vein, usually before breakfast, and was studied by methods outlined in another article. Proteins were determined on 0.5 cc samples of plasma or serum by the ordinary Kjeldahl procedure. In all the earlier studies plasma was employed, in the more recent experiments serum was used. In the interests of economy blood and not plasma or serum was taken for the estimation of nonprotein nitrogen.

In the tables the first column shows the caloric value of the diet and the second the fluid intake. The latter includes all obvious fluids given at or between meals, but not the fluid content of solid or semisolid foods. In Column 3 is given the urine volume, while Column 4 presents the fluid balance as intake — output. In the next column appears the weight in kilograms. In each case the weight given for a certain day is the one obtained the next morning and, therefore, indicates the result of the treatment of the day in question. The nitrogen intake is obtained by dividing the protein of the diet by 6.25. The nitrogen output represents only the amount excreted in the urine. The difference, which appears in the next column, indicates the excess of food nitrogen over urinary nitrogen. Nonprotein nitrogen of the urine was estimated only in a few cases. This is a measure of the actual nitrogen catabolism. The difference between the food nitrogen and the urinary nonprotein nitrogen represents the amount of protein given in excess of the actual metabolic needs of the individual. Protein lost as albumin is obtained by subtracting urinary nonprotein nitrogen from urinary total nitrogen and multiplying the difference by 6.25. The difference between chlorid intake and output has been given as a general indication of the trend of the chlorid balance. Chlorid has been expressed in the usual manner, as sodium chlorid. When it was desired to increase the chlorid of the diet the additional salt was given to the patient in capsules to be taken in that form or to be spread on the food, according to his tastes. When ammonium chlorid or urea was given the additional nitrogen and chlorid from these sources has been estimated and added to the figures for daily intake.

$$\begin{aligned}
 1 \text{ gm of ammonium chlorid} &= \frac{14}{53.5} = 0.262 \text{ gm of nitrogen and } \frac{58.5}{53.5} = \\
 &0.262 \text{ gm of sodium chlorid} \\
 1 \text{ gm of urea} &= \frac{28}{60} = 0.467 \text{ gm of nitrogen}
 \end{aligned}$$

REPORT OF CASES

CASE 1—A Polish man, aged 29, was admitted to the hospital, Oct 14, 1924, complaining of dyspnea, swelling of the legs and abdomen and lumbar pain.

About two years earlier he had an attack of rheumatism involving the wrists, ankles and shoulders, which ran a remittent course for three or four months, shifting from joint to joint. Shortly after the rheumatism disappeared,

the ankles began to swell and the legs and abdomen later became involved. At the same time he noticed that his urine was bloody and he developed frequency of urination and pain in the lumbar region. All these symptoms persisted with slight remissions and exacerbations. The latter occurred especially when he caught cold or had a sore throat. During the periods of increasing edema, there was weakness, general irritability, sleeplessness and frequent night sweats. For six months dizziness, occasional frontal headaches and dyspnea on exertion, and for three or four months a nonproductive cough and a tendency to gastric distention after eating also had troubled him.

As a child in Poland he had typhus, he could remember no other serious illnesses and none of the usual childhood diseases. For some years he had frequent attacks of tonsillitis. In 1918, while he was serving in the French army, one tonsil was removed. At that time he was ill for about a month and received three therapeutic injections of some kind, apparently not mercury or arsenicals. His second tonsil was removed about six months before he entered the hospital. His habits were quite exemplary and he said that he had no venereal disease.

When he entered the hospital he appeared chronically ill, he was pale and sallow, with slight puffiness of the face. The temperature, pulse and respirations were normal. His heart was slightly enlarged to the left and a loud systolic murmur was audible over the whole precordium. The systolic blood pressure was 155, the diastolic 95. The peripheral vessels were soft. At the base of both lungs resonance and breath sounds were impaired and there were signs of slight accumulation of fluid in the peritoneal cavity. The liver edge was felt just below the costal margin and the edge of the spleen descended 2 cm below the costal margin on deep inspiration. There was considerable tenderness to deep palpation and percussion in both costovertebral angles, but the kidneys did not seem to be enlarged. Over the whole trunk there was moderate pitting edema, and a more striking edema of the lower extremities.

Ophthalmoscopic examination revealed slight irregularity in the outlines of the arteries. The blood Wassermann reaction was negative. Phenolsulphonephthalein excretion, October 15, was 45 per cent in two hours and ten minutes. Blood cultures on October 15 and 19 were sterile. Urine cultures also proved sterile. Roentgen-ray examination of the heart revealed slight left sided enlargement. The basal metabolism, October 16, was 125 per cent above normal. On admission the urine contained a large amount of albumin, many hyaline and granular casts and numerous red and white blood cells.

The patient was immediately ordered a salt-poor diet containing 50 gm of protein and 2,200 calories, with fluids restricted to 2,000 cc. This resulted in diuresis. By October 20 most of the subcutaneous edema and all signs of ascites had disappeared. The spleen was no longer palpable, although the area of splenic dullness was still enlarged. October 25, no signs of edema could be found. The character of the urine was, however, unchanged. During this period and until the middle of November, in spite of the fact that the patient was losing weight, the relation of fluid intake to urine output indicated a considerable positive water balance. The explanation probably lies in the fact that he had frequent, profuse night sweats.

Because he had a constant negative nitrogen balance with a diminishing blood nonprotein nitrogen, his diet was increased to contain 75 gm of protein and 2,500 calories, November 24. On this diet he began to store nitrogen but the nonprotein nitrogen of the blood rose.

In view of a continuous negative salt balance 5 gm of sodium chloride was given daily, beginning October 28. On this regimen the weight again increased and considerable salt was retained in the body. It must be mentioned that during this period he developed some temperature, associated with backache and gross hematuria.

November 8, the salt-poor diet was resumed. By November 13 the blood nonprotein nitrogen had diminished again without any reduction of dietary

protein and in spite of a positive nitrogen balance. He was then given a course of ammonium chlorid therapy. In spite of a severe acidosis this produced no considerable diuresis, but the albuminuria increased in severity. For three days after the ammonium chlorid was discontinued he suffered from epigastric discomfort that prevented him from eating his full diet. At this time he developed a definite diuresis.

November 22, the protein of the diet was reduced to 60 gm, and it was kept at this level until he left the hospital. Under this regimen he stored nitrogen constantly. At first he lost weight, probably the residuum of his edema. November 29, the caloric value of the diet was increased to 3,500 calories. Under these conditions his weight increased slightly and he stored nitrogen constantly in spite of the fact that he remained free from edema and that the blood nonprotein nitrogen diminished.

The urine albumin, casts and cells decreased somewhat during this period. He was discharged from the hospital December 24.

From time to time his temperature rose somewhat above normal, usually with symptoms of upper respiratory tract infection. October 26, it went up to 100.4 degrees F, November 8 and again on December 17, as high as 101, and on each of the last four days in the hospital it reached 100 F.

At the time of admission he presented a considerable degree of anemia of the secondary type. The hemoglobin determined gasometrically by the Van Slyke method was only 53 per cent (99 per cent by volume oxygen capacity), the cell volume 24.8 per cent by volume, and the red blood cell count about 4 million. The blood picture varied somewhat, but at the time of discharge was distinctly improved. The hemoglobin had risen to 65 per cent and the cell volume to 28.4 per cent by volume.

The specific gravity of the twenty-four hour specimen varied from 1.009 to 1.024. Throughout the course of the disease his urine contained large amounts of albumin and casts and some red blood cells and leukocytes. The number of cells varied greatly. The metabolism record appears in Table 1.

During the whole time he was studied in the hospital, sixty-four days, he received altogether protein and ammonium chlorid equivalent to 688.3 gm of nitrogen. Over the same period he excreted in the urine 568.5 gm of nitrogen, giving a positive balance of 119.8 gm. This does not, of course, represent the actual amount of protein stored because the amount of nitrogen lost in the stools has been neglected. The latter usually amounts to about 10 per cent of the food protein. The actual food protein amounted to the total nitrogen intake minus 18.1 gm of nitrogen which was given as ammonium chlorid, or $688.3 - 18.1 = 670.2$. Therefore, $670.2 \times 0.9 = 605$ = the grams of nitrogen actually available to the body as useful protein. The nitrogen of the ammonium chlorid was presumably recovered in the urine as urea and ammonium salts. In calculating the nitrogen balance it is therefore necessary to subtract the same amount from the urinary nitrogen. The urinary nitrogen actually observed was 568.5 gm. Corrected for ammonium chlorid and urea this becomes $568.5 - 18.1 = 550.4$ gm. The nitrogen balance is, therefore, $605 - 550.4 = 54.6$ gm of nitrogen retained, the equivalent of $54.6 \times 6.25 = 341$ gm of protein, or, dividing by the number of days, $\frac{341}{64} = 5.3$ gm of protein per day. In other words, by the administration of an average of $\frac{670.2 \times 6.25}{64} = 65.4$ gm of protein per day, the patient was enabled to store 5.3 gm per day for a period of more than two months.

When he entered the hospital the patient had evident edema and part of his weight, 71.8 kg, was probably made up by tissue that was relatively inactive from a metabolic standpoint. His weight at the time of discharge, 64.5 kg, represents more accurately the amount of functioning tissue. In calculating the rate of metabolism this terminal weight has, therefore, been employed throughout this study. On this basis the protein given amounted to $\frac{65.4}{64.5} = 1.02$ gm per kilogram a day.

TABLE 1—Data in Case 1

Date	Food, Calories	Fluids		Weight, Kg	Total Nitrogen			Urine Non- protein as Albu- min, Gm	Protein Lost as Albu- min, Gm	Chlorid is			Blood		Special Medication
		Intake, C c	Urine, C c	Balance, C c	Intake, Gm	Urine Gm	Balance, Gm			Intake, Gm	Output, Gm	Balance, Gm	Nonprotein Nitro- gen, Mg per 100 C c	Plasma Protein, per Cent	
Oct 16	2,279	2,000	840	1,160	71.5	8.52	7.13	1.39	9.4	1.07	4.23	-3.16	43	4.56	
17	2,250	2,100	1,350	750	70.3	8.05	11.83	-3.78	15.7	1.35	8.71	-7.36			
18	2,279	1,800	760	1,040	69.9	6.69	1.50	5.36	8.3	1.21	5.39	-4.18			
19	2,279	2,000	1,620	380	69.6	8.19	-9.07	12.65	28.8	1.21	9.17	-7.96			
20	2,250	2,000	1,320	680	69.1	8.19	-1.30	7.10	14.9	1.21	5.52	-4.31			
21	2,259	2,000	490	1,510	68.8	8.19	4.32	3.22	16.9	1.21	2.19	-0.98			
22	2,279	2,000	1,110	890	67.2	8.19	8.83	6.76	12.9	1.21	5.16	-3.95	35	4.38	
23	2,259	2,000	940	1,060	66.8	8.19	-1.33	7.10	15.1	1.21	3.93	-2.72			
24	2,564	1,920	1,020	900	66.0	12.16	10.62	1.54	16.2	1.19	4.31	-3.12			
25	2,539	2,000	980	1,020	65.8	11.76	10.68	1.08	16.2	1.05	3.65	-2.60			
26	2,536	2,100	870	1,230		12.30	9.60	2.70	14.9	1.30	2.87	-1.57			
27	2,539	2,000	890	1,110	64.4	11.76	10.32	1.44	15.3	1.05	3.26	-2.21			
28	2,762	2,000	515	1,485	64.8	12.51	5.81	6.70	8.1	6.10	1.61	4.49	51	3.91	
29	2,637	1,820	860	960	64.9	12.11	9.33	2.78	12.7	6.21	4.80	1.41			
30	2,536	2,030	1,060	970	64.4	12.30	12.88	-0.58	20.6	6.30	4.35	1.95			
31	2,558	2,030	1,050	980	65.7	12.41	11.44	0.97	15.2	6.30	5.25	1.05			
Nov 1	2,564	2,000	630	1,350	63.2	12.16	7.55	4.61	11.4	6.19	3.99	2.20			
2	2,537	2,000	760	1,240	65.7	12.17	8.49	3.63	11.8	6.21	3.55	2.66			
3	2,558	2,000	640	1,330	65.5	12.41	7.61	4.80	8.2	6.30	2.81	3.49			
4	2,667	2,000	760	1,240		8.52	9.37	-0.85	14.6	5.86	3.33	2.53			
5	2,784	2,020	660	1,360	65.3	11.85	7.99	3.86	14.6	6.03	3.43	2.60	53	3.62	
6	2,764	2,090	900	2,090	66.6	12.01	10.67	1.34	15.7	6.16	4.95	1.21			
7	2,771	3,030	900	2,130	67.3	12.32	10.39	1.93	16.2	6.04	4.52	1.52			
8	2,764	1,980	810	1,170	68.0	12.01	9.56	2.45	4.8	1.16	4.02	-2.86			
9	2,771	2,070	700	1,370	68.0	12.32	8.32	4.00	13.5	1.04	2.91	-1.87			
10	2,774	2,130	1,050	1,080	68.0	12.34	11.68	0.66	16.9	1.08	4.42	-3.34			
11	2,769	2,090	750	1,340	68.1	12.32	8.69	3.63	13.6	1.15	3.27	-2.12			

12	2,762	2,000	800	1,200	67 1	12 24	9 64	2 70	7 21	15 2	1 32	3 70	-2 28	43	4 17	Ammonium ehlorid, 10 gm
13	2,774	2,020	940	1,080	67 5	14 96	10 89	4 07	8 24	16 6	12 01	4 95	7 06			Ammonium ehlorid, 10 gm
14	2,930	2,000	1,170	830	67 5	14 55	12 68	1 87	9 68	18 7	12 17	6 86	5 31			Ammonium ehlorid, 15 gm
15	2,769	2,000	1,340	660	67 5	16 25	13 78	2 47	10 00	23 6	17 55	8 55	9 00			Ammonium ehlorid, 15 gm
16	2,737	2,000	1,500	500	67 9	12 45	13 43	-0 98	10 77	16 6	17 26	8 26	9 00			Ammonium ehlorid, 15 gm
17	2,690	2,000	1,380	620	68 7	15 86	10 96	4 90	7 64	20 8	11 44	7 82	9 62			Ammonium ehlorid, 15 gm
18	2,769	2,000	1,290	710	68 2	13 36	10 17	3 19	7 03	19 6	5 53	7 28	-1 75		4 39	Ammonium ehlorid, 15 gm
19	2,666	2,000	1,060	940	67 1	9 84	8 62	1 22	6 03	16 2	1 06	5 47	-4 41			Ammonium ehlorid, 4 gm
20	2,625	2,000	1,400	600	65 5	11 28	9 99	1 29	7 44	15 9	1 00	7 17	-6 17			
21	2,531	2,000	1,980	20	64 5	10 77	10 19	0 58	9 65	3 4	0 95	9 72	-8 77			
22	2,871	2,000	2,340	-340	64 5	9 55	10 86	-1 31	8 22	16 5	0 99	11 51	-10 52			
23	2,835	2,000	1,160	-160	63 2	9 63	10 25	-0 62	7 58	16 7	0 88	10 00	-9 12			
24	2,812	2,000	1,740	260	62 5	9 48	9 64	-0 16	6 68	18 5	0 92	8 12	-7 20			
25	2,835	2,000	1,420	580	62 7	9 60	9 02	0 53	6 31	16 9	0 88	6 42	-5 54		4 07	
26	2,871	2,000	1,480	520	62 5	9 55	9 03	0 52	6 41	16 4	0 99	7 07	-6 08			
27	2,831	2,000	1,270	730	62 5	9 82	8 54	1 28	6 11	15 2	0 98	5 07	-4 09			
28	3,661	2,000	1,120	880	62 5	9 85	7 03	2 82	4 96	12 9	1 04	3 70	-2 66			
29	3,538	2,000	1,260	740	62 6	9 96	7 10	2 86	5 35	10 9	1 10	3 72	-2 62			
30	3,521	2,000	910	1,090	62 7	10 16	6 74	3 42	4 92	11 4	1 29	3 62	-2 33			
1	3,618	2,000	940	1,060	63 2	10 45	6 37	4 08	4 74	10 2	0 98	3 86	-2 88			
2	3,487	2,000	1,540	460	62 9	9 60	7 16	2 44	5 53	10 2	1 14	4 73	-3 59			
3	3,535	2,000	1,340	640	63 4	9 96	6 84	3 12	5 06	11 1	1 10	3 11	-1 97			
4	3,487	2,000	1,240	760	63 4	9 70	6 77	2 83	5 27	9 4	1 14	3 76	-2 74			
5	3,531	2,000	1,580	420	63 2	9 92	6 57	3 35	5 70	5 4	1 02	3 39	-2 11			
6	3,618	2,000	1,680	320	63 5	10 45	8 28	2 17	5 88	15 0	0 98	3 39	-2 11			
7	3,487	2,000	1,420	580	63 4	9 60	6 29	3 31	4 96	8 3	1 14	3 31	-2 17			
8	3,531	2,000	1,140	560	63 3	9 92	8 02	1 90	6 18	11 5	1 02	3 05	-2 03			
9	3,521	2,000	1,220	780	63 5	10 16	7 20	2 96	4 85	14 6	4 29	3 62	0 67			
10	3,538	2,000	980	1,020	64 2	9 96	7 06	2 90	5 32	10 9	4 10	4 08	0 02			
11	3,487	2,000	980	1,020	64 2	9 60	6 79	2 81	5 03	10 9	1 14	4 63	-3 49			
12	3,531	2,000	1,050	940	64 0	9 92	6 37	3 55	4 65	10 7	1 02	3 88	-2 86			
13	3,521	2,000	1,160	840	64 0	10 16	6 79	3 37	5 12	10 4	1 29	1 31	-3 02			
14	3,538	2,000	1,300	700	64 7	9 96	6 85	3 11	5 02	11 4	1 10	3 90	-2 80			
15	3,521	2,000	1,220	780	64 6	10 16	6 66	3 50	4 98	10 5	1 29	3 27	-1 98			
16	3,487	2,000	1,220	780	64 1	9 60	6 48	2 13	4 79	10 6	1 11	2 89	-1 77			
17	3,618	2,000	770	1,230	64 0	10 45	5 76	4 69	4 28	9 2	0 98	2 52	-1 54			
18	3,521	2,000	1,420	580	64 5	10 16	7 39	2 57	6 01	9 9	1 29	3 81	-2 52			

The amount of protein lost as albumin in the urine amounted to 862.5 gm, or $\frac{862.5}{64} = 13.5$ gm a day. By the administration of 102 gm of protein the patient was enabled to maintain nitrogen equilibrium in spite of the continuous loss of 13.5 gm of protein a day as albumin, and to store 5.3 gm of protein a day. This calculation is probably minimal. The nitrogen output was partly due merely to sweeping out of the excessive nonprotein nitrogen of the blood and partly due to the loss of nonprotein nitrogen in the edema fluid that was lost through diuresis.

The actual nitrogenous metabolism of the individual is expressed not by the total nitrogen output, but by the excretion of nonprotein nitrogen. This amounted altogether to 430.3 gm in sixty-four days. From this must be subtracted the nitrogen given as ammonium chloride and the amount due merely to the loss of edema fluid and the reduction of the blood and tissue nonprotein nitrogen. For the purpose of gaining some estimate of the value of the two latter factors one may assume that the nonprotein nitrogen is comparatively evenly distributed throughout the aqueous phase of tissues and body fluids. Under normal circumstances about 70 per cent of the body weight is composed of water. The concentration of water in edema fluid is usually much greater, at least 90 per cent. If the final weight of the patient, 64.5 kg, is considered to represent normal tissue and weight in excess of this edema, one may calculate the nonprotein nitrogen content of the whole body at the beginning of the experiment as 70 per cent of the final weight plus 90 per cent of the difference between initial and final weights, together multiplied by the initial blood nonprotein nitrogen, or $0.48 [(0.7 \times 64.5) + (0.9 \times 71.8 - 64.5)]$, and the nonprotein nitrogen content of the body at the end of the experiment at 70 per cent of the final weight multiplied by the final blood nonprotein nitrogen, or $(0.7 \times 64.5) \times 0.28$. The difference between these two represents what may be termed the extra metabolic loss of nonprotein nitrogen. This equals $0.48 [(0.7 \times 64.5) \times (0.9 \times 71.8 - 64.5)] - 0.28 (0.7 \times 64.5)$. This can be simplified to the form $(0.48 - 0.28) (0.7 \times 64.5) + (71.8 - 64.5) (0.9 \times 0.48)$, i. e., 70 per cent of the final weight multiplied by the change of nonprotein nitrogen plus 90 per cent of the change of weight multiplied by the initial nonprotein nitrogen. This is equal, in this case, to 12.2 gm. If this is added to the ammonium chloride nitrogen equivalent, 18.1 gm, and the sum of the two is subtracted from the total nonprotein nitrogen, the difference represents the excretion of nitrogen derived from actual protein catabolism. Or, $430.3 - (18.1 + 12.2) = 400$ gm of nitrogen catabolized in sixty-four days, or $\frac{400}{64} = 6.3$ gm of nitrogen a day. This is equivalent to 6.3×6.25 gm of protein a day, or $\frac{39.4}{64.5} = 0.61$ gm of protein per kilogram per day.

A considerable amount of space has been devoted to the explanation of the calculations of this period in order to make the processes clear to the reader. The same methods have been employed in subsequent calculations. The summarized results appear in Table 2. Of course, these methods of correction are subject to a considerable error that cannot be evaluated. The conclusions drawn from the work would not be qualitatively altered if all corrections had been omitted. The corrections are in the right direction and the fact that the application of such corrections does not significantly affect the conclusions gives the latter a validity that they would otherwise lack.

These average figures do not represent the actual course of the metabolism while the patient was in the hospital nor do they give any idea of the effects of the various therapeutic measures employed. For purposes of further analysis his course has been divided into three periods, during each of which he received a different diet. The first of these lasted from October 16 to 23, inclusive. During these eight days he was given about 50 gm of protein, 2,250 calories and 2,000 cc of fluid daily, with a minimum amount of salt.

TABLE 2—Summary of Case 1

Period	Number of Days	Dates, Inclusive	Calories per Day	Calories per Kg per Day	Nitrogen Intake, Gm	Protein, per Kg per Day, Gm	Available Food Nitrogen, Gm	Total Nitrogen Balance					Protein Catabolism per Kg, Gm per Day	Protein Lost as Albumin, Gm per Day
								Urinary Nitrogen, Gm	As Nitro gen, Gm	As Protein, Gm per Day	Urinary Nonprotein Nitrogen Gm	Nitrogen Catabolism, Gm		
1	8	Oct 16 to 23	2,260	35	65.7	0.80	59.1	75.1	-16.0	-12.0	57.1	51.3	0.62	11.0
2	26	Oct 16 to Nov 18	2,600	40	127.5	1.14	309.1	224.1	11.2	8.2	200.1	188.3	0.70	15.0
3	30	Nov 18 to Dec 15	3,200	51	209.1	0.96	269.2	230.8	38.1	8.0	17.1	162.9	0.50	12.0
Total	64	Oct 16 to Dec 18			670.2	1.07	650.0	530.1	51.6	5.0	130.3	402.6	0.61	13.5

During the second period of twenty-six days, October 24 to November 19, inclusive, he received about 75 gm of protein and 2,600 calories. During the greater part of this period he was given an additional 5 gm of salt daily, and from November 13 to 18 he received ammonium chlorid.

During the last period of thirty days, from November 19 to December 18, inclusive, he was given about 60 gm of protein and 3,500 calories.

In the first period he received 65.7 gm of nitrogen in the food, or $\frac{65.7 \times 6.25}{8} = 51.3$ gm of protein a day, or $\frac{51.3}{64.5} = 0.8$ gm of protein per kilogram a day, and 2,260 calories per day, or $\frac{2260}{64.5} = 35$ calories per kilogram a day. Subtracting for loss in stools 10 per cent of the food nitrogen, the available nitrogen in food becomes $0.9 \times 65.7 = 59.1$ gm. The urinary excretion at the same time was 75.1 gm, giving a negative balance of -16 gm, or 2 gm a day, the equivalent of $2 \times 6.25 = 12.5$ gm of protein. During the same period he excreted 112 gm of protein, or 14 gm a day in the urine as albumin. The nonprotein nitrogen excretion was 57.1 gm. This must be corrected for a weight loss of $71.8 - 66.8 = 5$ kg and a reduction of blood nonprotein nitrogen from 43 to 35 mg per cent. The correction amounts to $(64.5 \times 0.7) (0.43 - 0.35) + 0.9 [0.43 (71.8 - 64.5) - 0.35 (66.8 - 64.5)] = 5.8$ gm. The actual nitrogen catabolism, therefore, amounted to $57.1 - 5.8 = 51.3$ gm. This is equivalent to $\frac{51.3 \times 6.25}{8} = 40.1$ gm of protein a day, or $\frac{40.1}{64.5} = 0.62$ gm of protein per kilogram a day.

It is therefore evident that the administration of 0.8 gm of protein and 35 calories per kilogram a day did not suffice to prevent this patient from wasting his own body proteins. At the same time the failure to attain equilibrium on this diet was due neither to an unduly high rate of metabolism nor to a toxic destruction of protein. The diet provided quite amply for the ordinary metabolic requirements, which amounted to less than the average two-thirds gram per kilogram. The surplus of protein, however, was insufficient to cover the protein lost as albumin in the urine.

During the second period he received in his diet and as ammonium chlorid 327.5 gm of nitrogen. Corrected for 18.1 gm of ammonium chlorid nitrogen this becomes $327.5 - 18.1 = 309.4$ gm, or $\frac{309.4 \times 6.25}{26} = 74.4$ gm of protein a day, or 1.14 gm of protein per kilogram a day. After correction for nitrogen lost in the stools, the available protein nitrogen of the food comes to $0.9 \times 309.4 = 278.6$ gm. The urinary nitrogen excretion, also corrected for ammonium chlorid amounted to $262.5 - 18.1 = 244.4$ gm, leaving a positive nitrogen balance of 34.2 gm, or $\frac{34.2 \times 6.25}{26} = 8.2$ gm of protein a day. The protein lost as albumin during the same period amounted to 389.9 gm, or 15 gm a day. The urinary nonprotein nitrogen output was 200.1 gm. This must be corrected for 18.1 gm of ammonium chlorid nitrogen, an increase of 1.4 kilograms of body weight and a rise of blood nonprotein nitrogen from 35 to 47 mg per cent. The correction for rise of blood nitrogen and gain of weight equals $(64.5 \times 0.7) (0.47 - 0.35) + 0.9 [0.47 (68.2 - 64.5) - 0.35 (66.8 - 64.5)] = 6.3$ gm. The true catabolic nitrogen, therefore, equals $200.1 - 18.1 + 6.3 = 188.3$ gm. This is equivalent to $\frac{188.3 \times 6.25}{26} = 45.3$ gm of protein a day, or 0.7 gm of protein per kilogram a day.

At first sight it appears that the administration of a larger excess of protein has, in this case, effectually prevented protein wastage, but only by increasing the protein catabolism and causing the edema and the

blood nonprotein nitrogen to increase. This was the point of view which was taken at the time and which led to reduction of the diet in the third period. In retrospect such an explanation appears less satisfactory. Throughout the whole of the first two periods the patient had profuse night sweats and occasional bouts of fever. These became more serious during the second period and were associated with attacks of lumbal pain and gross hematuria. These symptoms were probably evidences of an exacerbation of the disease which might have occurred whether the diet had been altered or not. The course of his illness was throughout marked by such attacks.

During the last period, the nitrogen intake amounted to 299.1 gm, or $\frac{299.1 \times 6.25}{30} = 62.3$ gm of protein a day, or $\frac{62.3}{64.5} = 0.96$ gm of protein per kilogram a day and 3,290 calories a day, or 51 calories per kilogram a day. The nitrogen intake, corrected for loss in stools, was $0.9 \times 299.1 = 269.2$ gm. The urinary nitrogen excretion came to 230.8 gm, leaving a positive balance of 38.4 gm, or $\frac{38.4}{30} = 1.28$ gm of nitrogen a day, the equivalent of 8 gm of protein. The protein lost as albumin during the same period amounted to 360.6 gm, or $\frac{360.6}{30} = 12$ gm a day. The urinary nonprotein nitrogen output was 173.1 gm. The weight fell to 37 kg and the blood nonprotein nitrogen diminished from 47 to 28 mg per cent. The correction for fall of weight and blood nonprotein nitrogen amounted to $(64.5 \times 0.7) (0.47 - 0.28) + (68.2 - 64.5) (0.9 \times 0.47) = 10.2$ gm. The true catabolic nitrogen, therefore, equaled $173.1 - 10.2 = 162.9$ gm, the equivalent of $\frac{162.9 \times 6.25}{30} = 33.9$ gm of protein a day, or 0.53 gm per kilogram a day.

In the last period, then, by the administration of about a gram of protein per kilogram and a comparatively high caloric diet the patient was enabled to maintain a low level of nitrogen metabolism, to replace protein lost as albumin in the urine at the rate of 12 gm a day, and to restore the depleted tissues of the body at the rate of 8 gm or more of protein a day. It is not at all improbable that the lower protein of the first period would have resulted in the attainment of nitrogen equilibrium if it had been supported by more carbohydrate and fat calories. On the other hand, it is quite as possible that the higher protein metabolism of the earlier part of the course had no relation to the diet, but was an expression of a more serious clinical condition. It is worthy of special note that the level of blood nonprotein nitrogen varied in general with the rate of nitrogen metabolism.

One further point requires consideration. When the patient was admitted, he appeared comparatively well nourished. As the edema disappeared it became evident that his well fed look was entirely specious and that the real man beneath the edema was quite cachectic. It is surprising how much food he required to cause any healthy gain of weight in spite of the fact that his metabolism was normal. How much of his cachexia was attributable to previous misdirected diet and how much to the inherent character of the disease it is impossible to

say The fact that he was able to store so much protein for so considerable a time is itself convincing evidence that there had been previous protein starvation If it is assumed that protein makes up as much as 25 per cent of muscle tissue the amount of protein retained in the sixty-four days in the hospital represents $\frac{341}{0.25} = 1,364$ gm of muscle tissue This gain, of course, masks to a certain extent the effects of diuresis, which must have been greater than the observed weight loss would indicate

CASE 2—A Polish rubber worker, aged 43, married, was admitted to the hospital, Jan 10, 1925, complaining especially of swelling of the abdomen Aug 29, 1924, he developed a coryza and sore throat that kept him in bed for two weeks When he returned to work he noticed that his face, legs, genitals and abdomen, and especially the last, became swollen This subsided after rest in bed, only to return as soon as he resumed his normal activities He noticed at the same time that he was more comfortable sitting up or reclining on two pillows than he was in the recumbent position, although he was not noticeably short of breath About the beginning of November he went to another hospital, the edema disappeared rapidly after rest and medication He was discharged after twelve days As soon as he left the hospital, edema, slight orthopnea and weakness recurred At no time did he notice hematuria, dysuria or nocturia, but he had been troubled somewhat with diurnal frequency

On admission he appeared somewhat pale and sallow, but large, well developed and fairly well nourished His face was somewhat puffy His pharynx and tonsils were injected and red, but there were no evidences of an acute inflammatory process Over the bases of both lungs there were dulness, diminished breath sounds and râles, extending somewhat higher on the right side than on the left The heart was not enlarged and presented no significant abnormalities, the systolic blood pressure was 122, the diastolic 78 The pulse was regular, of good quality and quite slow (50 per minute), respirations were quiet and normal in rate and rhythm The abdomen was distended, with signs of considerable ascites The genitals were markedly swollen and there was slight pitting edema of the backs of the legs and thighs and over the sacrum Otherwise physical examination revealed no abnormalities Ophthalmoscopic examination showed no signs of retinitis or vascular disease

The blood Wassermann reaction was negative Roentgen-ray examination of the chest showed no cardiac enlargement and no signs of pulmonary disease Phenolsulphonephthalein excretion, January 11, was 32 per cent in two hours and ten minutes An electrocardiogram, January 14, showed no abnormalities

He was given a salt poor diet containing about 60 gm of protein and 2,500 calories with fluids limited to 1,500 cc On this regimen he lost little weight, so he was given a course of ammonium chlorid This resulted in some diuresis, but at the end of the treatment he complained of pain and tenderness in the lumbar region on both sides and ran a temperature for two days (100.4 F, January 23, and 102.6 January 24)

The urine was cultured, January 20 and again January 26 On both occasions every specimen contained a gram-negative, nonmotile bacillus that produced no acid on most sugars This organism was not agglutinated by the patient's serum February 11, the phenolsulphonephthalein excretion was 40 per cent in two hours and ten minutes

After the first course of ammonium chlorid diuresis continued for two or three days and then ceased He was therefore given another course, beginning January 29 This was less effective than the first It was, however followed by a period of gradually diminishing weight

February 14, another course of ammonium chlorid was started without effect. From time to time after this he was given urea with little noticeable effect. All obvious edema was gone, but there was some swelling of the feet after he had been up and about for a while.

Roentgen-ray examination of the kidneys, March 13, revealed no evidences of enlargement or calculus formation.

March 17, tonsillectomy was performed under local anesthesia. In the next three days he lost 2 kg of weight, which caused the disappearance of the last vestiges of edema. After this his general condition improved steadily.

Blood counts showed a low grade anemia. On admission there were 4.5 million red cells and about 100 per cent of hemoglobin. On discharge, in spite of his improvement, the red cells had fallen to 3.4 million, and the hemoglobin to 85 per cent (Haldane scale).

The urine on admission contained many casts and red blood cells and moderate numbers of leukocytes. Occasionally it appeared grossly bloody. The cells diminished in numbers as the patient improved and after the middle of March all signs of hematuria had disappeared.

Beside the febrile attack noted above, the temperature rose to 100.4 F, March 5. On both occasions he complained of slight sore throat and both times showed slight exacerbations of the hematuria.

The detailed metabolism data appear in Table 3 and are summarized in Table 4.

During the whole time he was studied in the hospital, ninety-two days, he received a total of 1,091.7 gm of nitrogen. Of this 34.3 gm was given as ammonium chlorid and 46.7 gm as urea. The actual amount of food nitrogen given was therefore $1,091.7 - (34.3 + 46.7) = 1,010.7$ gm, or $\frac{1,010.7 \times 6.25}{92} = 68.7$ gm of protein a day, or $\frac{68.7}{64.6} = 1.06$ gm per kilogram a day.

In order to find out whether the large positive nitrogen balance he exhibited could be attributed to an excess of nitrogen in the stools, the stools were analyzed for two separate four-day periods during the last two weeks of his stay in the hospital, and were found on both occasions to contain 1.9 gm of nitrogen a day. At that time he was receiving 12.5 gm of nitrogen a day in his food. He was therefore losing about 15 per cent of this food nitrogen instead of the usual 10. Whether he lost as much earlier in the course of his disease it is impossible to say, but it is unlikely that he lost more. For the purpose of calculation it will be assumed that 1.9 gm of nitrogen were excreted in the stools daily throughout the course of study. The actual available food nitrogen then becomes $1,010.7 - (92 \times 1.9) = 835.9$ gm.

The nitrogen output amounted to 723.6. If this also is corrected for ammonium chlorid and urea, it becomes $723.6 - (34.3 \times 46.7) = 640.5$ gm, which leaves a positive nitrogen balance of 195.4 gm, the equivalent of $\frac{195.4 \times 6.25}{92} = 13.3$ gm of protein a day. During the same period he excreted in the urine, as albumin, 962.5 gm of protein, or 10.4 gm a day. The nonprotein nitrogen output came to 572.1 gm, of which again 34.3 and 46.7 gm were derived from ammonium chlorid and urea, respectively. The blood nonprotein nitrogen fell from 61 to 30 mg per cent, and the body weight from 76.4 to 64.6 kg. The latter accounted for $(64.6 \times 0.7) - (0.61 - 0.30) + (76.4 - 64.6) - (0.9 \times 0.61) = 20.5$ gm. The actual catabolic nitrogen, therefore, amounted to $572.1 - (34.3 + 46.7 + 20.5) = 470.6$ gm, or $\frac{470.6 \times 6.25}{92} = 32$ gm of protein a day, or 0.5 gm of protein per kilogram a day.

The average level of protein metabolism in this case is surprisingly low, much lower than that of the first patient. The latter, however, had more continuous evidences of infection and received a lower caloric diet throughout.

TABLE 3—Data in Case 2

Date	Food, Calories	Fluids		Weight, Kg	Total Nitrogen			Urine Protein, Gm	Non-Protein Nitrogen, mg per 100 C c	Blood Nitro-gen, per Cent	Special Medication
		Intake C c	Urine, C c		Balance, C c	Intake, Gm	Urine, Gm				
Jan 12	2,512	770	1 010	-270	76 4	8 57	- 1 25	7 36	7 6		
13	2 554	1 000	690	310	77 3	9 91	3 91	4 86	7 1	61	4 03
14	2 542	1 230	1 060	170	76 2	9 82	1 00	7 13	10 6		
15	2,512	1,100	1,200	-10	76 6	8 98	0 84	7 38	10 0		
16	2,496	1,345	880	465	76 8	9 70	3 21	4 80	10 6		
17	2,542	1,470	1,285	185	76 8	8 6	1 06	7 17	9 9		
18	2,536	1 250	960	290	75 5	10 05	2 82	5 66	9 8		
19	2,542	1,080	1,370	560	75 7	9 82	0 66	7 08	13 0		
20	2,512	1 000	1,240	360	75 0	13 75	6 42	6 00	8 3	41	Ammonium chlorid, 15 gm
21	2,476	1,495	1,440	57	74 3	13 43	4 16	7 16	13 2		Ammonium chlorid, 15 gm
22	2,542	1,707	2,200	-315	73 9	13 75	-0 45	11 70	15 6	45	Ammonium chlorid, 15 gm
23	2,475	1,450	1,780	-330	72 7	9 16	-1 52	7 97	16 9		
24	2,542	1,470	1,360	110	72 3	9 82	0 03	6 81	18 6		
25	2,826	1,470	1 190	280	71 6	8 64	0 19	6 34	13 2		
26	2,486	1 325	980	345	71 2	9 35	3 69	4 70	7 3		
27	2,534	1,225	1 120	105	71 2	9 75	3 04	5 81	5 6		
28	3,284	1,765	1,020	745	70 6	9 92	3 94	5 11	5 4		
29	3,265	1,445	1 100	345	70 5	12 42	6 04	5 02	8 0		Ammonium chlorid, 10 gm
30	3,267	1,405	2,330	-925	70 0	12 37	-1 14	10 88	16 4		Ammonium chlorid, 10 gm
31	3,217	1,455	980	575	70 5	10 93	4 43	5 02	9 3		Ammonium chlorid, 5 gm
1	2,542	1,280	1,520	30	70 1	11 14	6 74	5 78	10 2		Ammonium chlorid, 5 gm
2	3,148	1,480	1,840	-640	70 4	11 14	1 22	7 67	14 1		Ammonium chlorid, 5 gm
3	3,148	1,450	1,220	230	69 7	11 35	4 27	5 09	12 4		Ammonium chlorid, 5 gm
4	3,091	1,545	1,380	165	69 7	11 03	2 01	6 31	16 9		Ammonium chlorid, 5 gm
5	3,056	1,865	1,220	645	69 5	9 11	1 63	6 10	10 5		Ammonium chlorid, 5 gm
6	3,153	1,485	1,110	375	69 2	10 08	1 86	6 08	9 0		Ammonium chlorid, 5 gm
7	3,169	1,435	1,145	290	68 8	10 29	1 33	7 22	10 3		Ammonium chlorid, 5 gm
8	3,190	1,340	1,474	-134	68 6	12 14	8 94	7 18	11 0		Urea, 5 gm
9	3,319	1,455	1,100	355	68 5	12 44	7 44	6 00	9 0		Urea, 5 gm
10	3,201	1,440	1,090	350	68 3	10 30	3 72	5 83	8 3		
11	3,169	1,105	1,355	-250	68 2	10 29	7 54	6 03	9 4		
12	3,194	1,495	900	595	68 3	10 00	6 17	5 15	9 4		
13	3,201	1,665	1,100	565	68 6	12 92	7 28	6 14	7 1	45	Ammonium chlorid, 10 gm
14	3,238	1,615	1,350	265	68 9	13 02	8 82	6 91	11 9		Ammonium chlorid, 10 gm
15	3,162	1,465	1,145	320	68 6	11 33	3 75	5 98	10 0		Ammonium chlorid, 6 gm
16	3,319	1,655	1,100	555	68 8	11 68	7 77	5 93	11 2		Ammonium chlorid, 6 gm
17	3,100	1 825	1 100	725	69 1	11 68	3 91	5 93	11 1		Ammonium chlorid, 6 gm
18	3 111	1 435	1,720	-285	68 4	10 79	1 11	7 48	13 7		Ammonium chlorid, 3 gm
19	3 175	1,935	1 170	765	68 9	9 42	6 63	5 12	9 4		
20	3,201	1 940	1 265	645	68 8	7 53	5 10	5 07	9 8		
21	3,288	1,965	1 290	735	68 8	10 40	2 62	6 08	10 6		
22	3 300	1,955	1,960	695	69 0	10 05	2 44	5 85	11 0		
23	3 375	1,975	1 100	875	69 0	9 42	2 27	5 60	10 3		
24	3 190	1 710	1 330	410	69 1	7 51	2 27	6 18	8 5		

[illegible]

The course of this case has again been divided into periods corresponding to different diets. The effect of ammonium chlorid and urea have been reserved for subsequent discussion and may be neglected for the present.

The first period of seventeen days, from January 12 to 28, inclusive, he received about 60 gm of protein and 2,500 calories daily, with 1,500 c c of fluid and minimum salt. During the second period of twenty-seven days, from January 29 to February 24, inclusive, the protein remained unchanged, but he was given additional fat and carbohydrate to make 3,150 calories. The third period of twenty days, February 25 to March 16, inclusive, he received 75 gm of protein and 3,530 calories and was allowed 2,000 c c of fluid. During the last period of twenty-six days, March 20 to April 15, inclusive, he continued the same dietary regimen. Three days have been omitted between the third and fourth periods. The first of these is the day on which tonsillectomy was performed. The metabolism of these periods and the totals for the whole study appear in Table 4.

The nitrogen intake during the first period of seventeen days was 176.5 gm, of which 118 gm was derived from ammonium chlorid, leaving a total food nitrogen of 164.7 gm or $\frac{164.7 \times 6.25}{17} = 60.6$ gm of protein a day, or 0.94 gm per kilogram a day. If $(19 \times 17) = 32.3$ gm is subtracted for loss in stools, the available food nitrogen becomes 132.3 gm. The nitrogen output in the urine = 143.3 gm, which must also be diminished by 118 gm as ammonium chlorid, leaving 130.5 gm and making a total positive nitrogen balance of 18 gm, or $\frac{18 \times 6.25}{17} = 0.66$ gm of protein a day. At the same time he lost as albumin in the urine 182.7 gm of protein, or 10.75 gm a day. The nonprotein nitrogen output was 113 gm, of which 118 gm was derived from ammonium chlorid and $(64.6 \times 0.7) (0.61 - 0.45) + 0.9 [0.61 (76.4 - 64.6) - 0.45 (70.6 - 64.6)] = 11.3$ gm is accounted for by reduction of blood nonprotein nitrogen from 61 to 45 mg per cent and a change of weight from 76.4 to 70.6 kg. The nitrogen actually catabolized, therefore, amounts to $113 - (118 + 11.3) = 89.9$ gm, which is equivalent to $\frac{89.9 \times 6.25}{17} = 33$ gm of protein a day, or $\frac{33}{64.6} = 0.51$ gm of protein per kilogram a day.

By the administration of 0.94 gm of protein per kilogram a day and 2,500 calories, then, it was just possible to maintain nitrogen equilibrium in the face of an albuminuria equivalent to 10.75 gm of protein a day, and this end was only attained by virtue of the fact that the nitrogen metabolism maintained a level below the normal average.

During the second period of twenty-seven days, he received 297.9 gm of nitrogen, of which 22.5 gm was given as ammonium chlorid and 7 gm as urea. If this is subtracted from the intake it leaves $297.9 - (22.5 + 7) = 268.4$ gm, the equivalent of $\frac{268.4 \times 6.25}{27} = 62.2$ gm of protein a day or $\frac{62.2}{64.6} = 0.96$ gm per kilogram a day, approximately what he received during the first period. However, he got 3,150 calories a day instead of the earlier 2,500.

If the nitrogen lost in the stools is subtracted from the food nitrogen, the available nitrogen comes to $268.4 - (27 \times 1.9) = 217$ gm. The urinary nitrogen excretion, corrected for ammonium chlorid and urea = $215.2 - (22.5 + 7) = 185.7$ gm, leaving a positive nitrogen balance of 32.3 gm, the equivalent of $\frac{32.3 \times 6.25}{27} = 7.5$ gm of protein a day. During the same time his albuminuria alone accounted for 286.2 gm of protein, or 10.6 gm a day. The nonprotein nitrogen output was 169.3. This must be corrected for ammonium chlorid, urea and change of weight from 70.6 to 69.1 kg. The blood nonprotein nitrogen was not estimated at the end of the period, but must have remained relatively constant because it was 45 mg per cent on both January 23 and February 13.

TABLE 4—*Summary in Case 2*

Period	Number of Days	Dates, Inclusive	Calories per Day	Calories, per Kg per Day	Nitrogen Intake, Gm	Protein, per Kg, per Day, Gm	Available Food Nitrogen, Gm	Total Nitrogen Balance				Protein Catabo- lism per Kg, Gm per Day	Protein Lost as Albumi- nuria, Gm per Day
								As Nitro- gen, Gm	As Protein, Gm per Day	Urinary Nitrogen Gm	Nitrogen Catabo- lism, Gm		
1	17	Jan 12 to Jan 28	2,500	39	176.5	0.94	132.3	1.8	0.7	113.0	89.9	0.51	10.8
2	27	Jan 29 to Feb 24	3,150	49	297.9	0.96	217.0	32.3	7.5	169.3	133.7	0.48	10.6
3	20	Feb 25 to Mar 16	3,530	55	273.4	1.21	211.4	64.2	20.0	137.3	107.2	0.52	10.8
4	26	Mar 20 to Apr 15	3,530	55	318.9	1.19	269.5	94.5	22.7	137.3	135.1	0.50	9.3
Total	92	Jan 12 to Apr 15			1,091.7	1.06	835.0	194.5	13.2	572.1	470.6	0.50	10.4

The loss of nonprotein nitrogen due to loss of body weight is equal to $(70.6 - 69.1) (0.9 \times 0.45) = 6.1$ gm. The actual nitrogen catabolism, therefore, amounted to $169.3 - (22.5 + 7.0 + 6.1) = 133.7$ gm, which represents $\frac{133.7 \times 6.25}{27} = 31$ gm of protein a day or $\frac{31}{64.6} = 0.48$ gm per kilogram a day.

It is therefore evident that by the addition of extra fat and calories it was possible to reduce the nitrogen metabolism and to increase the storage of protein in spite of the fact that the albuminuria remained practically constant.

During the third period of twenty days both calories and protein in the diet were increased and he was allowed as much as 2,000 c.c. of fluid a day. The total nitrogen intake amounted to 273.4 gm, of which 24 gm was given as urea. The actual food nitrogen was therefore $273.4 - 24 = 249.4$ gm, the equivalent of $\frac{249.4 \times 6.25}{20} = 77.9$ gm of protein a day, or $\frac{77.9}{64.6}$, or 1.21 gm per kilogram a day. After correction for loss in stools the available food nitrogen becomes $249.4 - (20 \times 1.9) = 211.4$ gm. The urinary nitrogen corrected for administered urea $= 171.2 - 24 = 147.2$ gm, leaving a positive balance of 64.2 gm, equivalent to $\frac{64.2 \times 6.25}{20} = 20$ gm of protein a day. The protein lost as albumin during the same period was 215.7 gm, which represented 10.8 gm of protein a day. The urinary nonprotein nitrogen was 137.3 gm. From this must be subtracted 24 gm for the urea given, and because the blood nonprotein nitrogen fell from 45 to 34 mg per cent and the body weight from 69.1 to 66.8 kg, in addition $(64.6 \times 0.7) (0.45 - 0.34) + 0.9 [0.45 (69.1 - 64.5) - 0.34 (66.8 - 64.6)] = 6.1$ gm. The actual nitrogen catabolism then came to $137.3 - (24.0 + 6.1) = 107.2$ gm, the equivalent of $\frac{107.2 \times 6.25}{20} = 33.5$ gm of protein a day, or 0.52 gm per kilogram a day.

The administration of an additional 15 gm of protein a day, therefore, resulted in a negligible increase of protein metabolism and an increase of protein storage almost equivalent to the added food protein. Meanwhile the albuminuria remained practically unchanged.

During the last period of twenty-six days, the diet remained unchanged. Meanwhile, however, the patient's tonsils had been removed. He received altogether 318.9 gm of nitrogen in this diet, that is, $\frac{318.9 \times 6.25}{26} = 76.6$ gm of protein a day, or $\frac{76.6}{64.6} = 1.19$ gm per kilogram a day. If the food nitrogen is corrected for loss in the stools, the available nitrogen becomes $318.9 - (26 \times 1.9) = 269.5$ gm. The urinary nitrogen, for the same period was 175 gm, leaving a positive balance of 94.5 gm, representing $\frac{94.5 \times 6.25}{26} = 22.7$ gm of protein a day, a surprisingly large amount. (It must be added that the operation, which was performed under procain anesthesia, was attended by no obvious change in rate of nitrogen metabolism.) The protein lost as albumin amounted to 242.1 gm, or $\frac{242.1}{26} = 9.3$ gm a day. The urinary nonprotein nitrogen amounted to 137.3 gm. The blood nonprotein nitrogen fell from 34 mg per cent and the weight from 64.8 to 64.6 kg. The actual nitrogen catabolism, therefore, amounted to $137.3 (64.6 \times 0.7) (0.34 - 0.30) + (64.8 - 64.6) (0.9 \times 0.34) = 135.4$ gm. This is equivalent to $\frac{135.4 \times 6.25}{26} = 32.5$ gm of protein a day, or 0.50 gm per kilogram a day.

The degree of nitrogen storage in this period is amazing. There is no evidence that the capacity of the organism for protein is diminishing.

On the contrary, if anything, it appears to be increasing. These changes were associated with marked clinical improvement, which was reflected in a diminution of albumin and disappearance of the last vestiges of hematuria and edema.

During the last few days the body weight increased somewhat without any evidences of edema. There can be little doubt that this gain represented a restitution of healthy tissue. There could be little doubt from the appearance of the patient at the end of his diuresis that he was actually wasted.

CASE 3—A Greek man, aged 30, was admitted to the hospital, Feb 2, 1924. Three months earlier he noticed that his feet and legs were swollen. The swelling increased gradually for a few days, but cleared up rapidly under Turkish bath treatment. Ten days before admission, when he awoke in the morning he found that the swelling had recurred and he had considerable difficulty in getting his shoes on. The edema increased gradually but steadily, without other symptoms, so that he was forced to stop work after about four days. He again tried the effect of a Turkish bath, but this time obtained no relief from the treatment. At no time had he noticed any symptoms other than the edema. He could recall no cold or other infection that could have precipitated the nephritis and gave no history of any previous diseases of importance.

When he entered the hospital he appeared well developed and nourished. The temperature was 99 degrees F, pulse 90 and respirations 20 a minute and quite normal in character, the systolic blood pressure was 154, the diastolic 85. The eyelids were somewhat puffy and there was a marked pitting edema involving the whole trunk, the genitalia and the lower extremities. There were signs of fluid in the right pleural and the peritoneal cavities. The liver and the spleen could not be felt and did not seem to be enlarged. There were no evidences of functional or organic heart disease. There was a small amount of exudate along the retinal vessels, but no other evidences of retinal changes. The blood count showed 4,800,000 red blood cells and 9,500 leukocytes, of which 71 per cent were polymorphonuclear neutrophils.

The blood Wassermann reaction was negative. The urine contained a large amount of albumin and casts of all kinds but no blood cells. The phenol-sulphonephthalein excretion was 55 per cent in two hours and ten minutes.

Cultures of the urine on two occasions obtained a nonhemolytic streptococcus, the first time in pure culture, the second time contaminated with *Staphylococcus albus*. He was placed on a diet containing 50 gm of protein and 2,000 calories with fluids limited to 1,500 cc per day (actually he took 1,000 cc or less). At the end of five days, as the edema had not diminished, the diet was made salt poor. Diuresis began at once, and by the end of four days, he had lost 8 pounds (3.6 kg) of weight. At this time, February 10, because he was hungry, his diet was increased to 60 gm of protein and 2,500 calories. Diuresis and loss of weight continued. The second examination of arterial blood was made before breakfast on the morning of February 14. The urine at this time contained considerable albumin and casts but no blood cells. The blood pressure had fallen to 115. Unfortunately, the urine specimens up to this time were not complete and the nitrogen, salt and water balances cannot, therefore, be calculated.

Under the same regimen he continued to lose weight for five days, although the character of the urine did not change. February 19, the addition to the diet of 3 gm of sodium chlorid was associated with an increase of the urine volume without any rise in the chlorid excretion. The last examination of arterial blood was made before breakfast of the day he was discharged from the hospital, February 23. The edema had by this time completely disappeared,

but the character of the urine was unaltered. The basal metabolism, February 9, was +16 per cent, February 16, it was -5 per cent. The results of the metabolism studies appear in Table 5.

The patient was unable to speak any English and it proved difficult to obtain his cooperation. For this reason the urine was lost daily throughout the earlier part of his course in the hospital. From February 14 on, with the exception of one day, complete collections were effected. This gave eight days of satisfactory study, the data for which appear in Table 5. During this period he received a salt poor diet containing about 60 gm of protein and 2,500 calories, with a low fluid intake. Diuresis proceeded for the first three days. At the end of this time the edema had disappeared completely.

During the eight days of study he received 768 gm of nitrogen in his food, representing 60 gm of protein a day, or about 1 gm per kilogram. Subtracting 10 per cent for loss in the stools, the available nitrogen becomes $768 - 77 = 691$ gm. The total urinary nitrogen amounted to 608 gm, leaving a positive balance of 83 gm, or $\frac{83 \times 6.25}{8} = 65$ gm of protein a day. At the same time he lost as albumin in the urine from 6 to 12 gm of protein a day. The urinary nonprotein nitrogen excretion was 237 gm for the four days that it was determined. During this time the weight fell about 2 kg and the blood non-

TABLE 5—Data in Case 3

Date	Food, Calories	Fluids			Weight, Kg	Total Nitrogen			Urine Nitro- gen, Gm	Pro- tein Lost as Albu- min, Gm	Urine Chlo- rid, Gm	Blood Nonpro- tein as Sodium Nitro- gen, Mg per 100 Cc	Plasma Pro- tein, Gm per Cent
		In take, Cc	Urine, Cc	Bal- ance, Cc		In take, Gm	Urine, Gm	Bal- ance, Gm					
14	2,500	800	1,340	-540	62.0	9.6	7.7	1.9	6.1	9.4	5.6	33	4.50
15	2,500	600			60.9	9.6							
16	2,500	600	630	-30	60.4	9.6	4.0	5.6	3.1	6.1	4.1		
17	2,500	600	1,300	-700	60.9	9.6	9.0	0.6	7.2	11.2	6.8		
18	2,500	800	1,900	-1,100	59.7	9.6	9.3	0.4	7.3	12.3	7.7		
19	2,500	600	1,380	-780	59.7	9.6	6.8	2.8			5.5		
20	2,500	800	1,040	-240	59.6	9.6	6.6	3.0			3.6		
21	2,500	600	1,380	-780	60.3	9.6	8.3	1.4			5.4		
22	2,500	650	1,380	-730	59.7	9.6	9.2	0.5			4.0	29	4.49
Total	20,000	5,450	10,350	-4,900		76.8	60.8	16.1			42.7		
Daily aver	2,500	681	1,294	-613		9.6	7.6	2.0	5.9	9.8	5.3		

protein nitrogen probably less than 4 mg per cent. Because of the uncertainty of these two changes, corrections have not been made for them. The rate of nitrogen catabolism calculated from the urinary nonprotein nitrogen amounts to $\frac{237 \times 6.25}{8} = 37$ gm of protein a day, or 0.62 gm per kilogram a day.

This patient again exhibited a comparatively normal rate of nitrogen catabolism and, by the administration of an excess of protein and adequate calories, was enabled to store protein in spite of a considerable albuminuria. Again this capacity for storage is an indication of previous protein starvation. Whether this was referable to an acceleration of general metabolism in the earlier stages of the disease or to a more profuse albuminuria or to insufficient diet can only be conjectured. While he was in the hospital, the basal metabolism fell from +16 per cent to -5 per cent. Unfortunately urinary studies of the earlier period are lacking.

CASE 4—A Polish man, aged 33, was first seen as an outpatient, Feb 8, 1924. One year before this, without any obvious cause, he developed puffiness of the ankles and occasional headaches. Two months' rest in bed resulted in no improvement. The edema varied somewhat in extent and severity, but never disappeared entirely. After about six months he began to have frequent attacks of severe headache, associated with vomiting. He had to urinate frequently during the day and during the night, but passed only small amounts at each voiding. From the onset he was troubled with excessive weakness and lassitude. He had no dyspnea, palpitation, precordial pain nor visual disturbances. Except that he had had rheumatism in 1916 and again in 1918, the past history was unimportant.

When he was first seen he weighed 79.7 kg. He appeared quite pale, his face was puffy, and there was moderate pitting edema of the legs. Respirations were quite normal. The heart was somewhat enlarged to the left and there was a faint systolic murmur at the apex. The systolic blood pressure was 180, the diastolic 110. The retina showed slight perivascular changes only. The urine contained a large amount of albumin, many casts and red blood cells, and a moderate number of leukocytes.

The first sample of blood was withdrawn, without stasis, from the arm vein before breakfast, February 13. At this time there was quite obvious edema of the legs and face. The urine was essentially negative.

March 10, he was admitted to the hospital and given a salt poor diet containing 50 gm of protein and 2,000 calories, with fluids limited to 1,500 cc. Diuresis began almost at once and was proceeding rapidly at the time the second blood examination was made, before breakfast on the morning of March 12. However, albuminuria was still profuse. The systolic blood pressure on admission was 168, the diastolic 110, March 13, the systolic was 144, the diastolic 96. The basal metabolism, March 12, was 45 per cent below normal.

The third examination of the blood was made before breakfast, March 22. By this time profuse diuresis had ceased, but he was still losing weight gradually. The systolic blood pressure was 122, the diastolic 84.

The fourth study was made before breakfast, April 5, the day he was discharged from the hospital. The edema had entirely disappeared. The phenolsulphonephthalein excretion was 38 per cent in two hours and ten minutes. The urine volume was adequate, and he was maintaining his weight at a constant level while receiving 2,500 cc of fluids. The basal metabolism, April 3, was —16 per cent.

He returned before breakfast, April 12, for another blood examination. His general condition was much improved. He had evidently gained considerable weight, but showed no signs of edema. He complained only of slight palpitation on exertion and the fact that he had to get up once or twice each night to urinate. His systolic blood pressure was 118, the diastolic 70. The urine contained only a trace of albumin, moderate numbers of casts and red blood cells. The results of metabolism studies appear in Table 6.

Unfortunately in this case also urine collections were incomplete during the early part of the hospital residence. For the last fourteen days, however, total nitrogen intake and output data are available. The diet was kept constant and contained 50 gm of protein and 2,000 calories a day. Diuresis continued in a moderate degree for the first days of this period.

The total nitrogen intake was 112 gm, equivalent to 50 gm of protein a day or 0.79 gm per kilogram a day. This becomes $112 - 112 = 100.8$ after correction for stools. The output was 119.4 gm, leaving a negative balance of $100.8 - 119.4$ gm, representing $\frac{18.6 \times 6.25}{14} = 8.3$ gm of protein per day. The urinary nonprotein nitrogen was not separately determined, so that neither the quantity of albumin lost nor the absolute protein catabolism can be estimated. The total nitrogen should be corrected for an increase of blood nonprotein nitrogen from 49 to 58 mg per cent and a change of weight from 66 to 63.4 kg.

This amounts to $(63.4 \times 0.7) (0.49 - 0.58) + (66 - 63.4) (0.9 \times 0.49) = 2.9$ mg
 This increases the actual nitrogen loss from 119.4 to 122.3 gm, and an actual negative balance of 21.5 gm equivalent to $\frac{21.5 \times 6.25}{14} = 9.6$ gm of protein a day

In this case the administration of 0.79 gm of protein per kilogram per day with 31 calories per kilogram failed to meet the metabolic requirements of the patient. Whether the negative balance was entirely due to albuminuria or was referable to a high protein catabolism cannot be determined from the data. Qualitative tests of the urine for albumin showed that the latter had decreased considerably during the period of study. That the general metabolism was not unduly elevated is evident from the fact that his basal metabolism on March 12 was 4.5 per cent below normal and during the latter part of the period of study had fallen to 16 per cent below normal.

TABLE 6—Data in Case 4

Date	Calories	Fluids			Weight, Kg	Total Nitrogen			Blood Nonprotein Nitrogen, Mg per 100 Cc	Plasma Protein, per Cent
		Intake, Cc	Urine, Cc	Balance, Cc		Intake, Gm	Urine, Gm	Balance, Gm		
March 22	2,000	1,300	1,020	280		8.0	7.7	0.3	49	6.06
23	2,000	1,400	1,000	400		8.0	8.0	0.0		
24	2,000	1,500	1,460	40	65.5	8.0	11.4	-3.4		
25	2,000	1,700	1,380	320		8.0	8.4	-0.4		
26	2,000	1,800	1,700	100		8.0	8.2	-0.2		
27	2,000	1,800	1,660	140		8.0	7.2	0.8		
28	2,000	1,850	1,030	820		8.0	5.9	2.1		
29	2,000	1,600	1,130	470		8.0	6.5	1.5		
30	2,000	1,600	1,980	-380		8.0	12.3	-4.3		
31	2,000	1,650	1,730	-80	64.2	8.0	7.9	0.1		
April 1	2,000	2,500	2,160	340		8.0	7.3	0.7		
2	2,000	2,400	2,600	-200		8.0	9.3	-1.3		
3	2,000	2,300	1,620	680		8.0	7.1	0.9		
4	2,000	2,200	1,670	530	63.4	8.0	7.4	0.6	58	5.88
Total	28,000	25,600	22,140	3,460		112.0	119.4	-7.4		
Daily aver	2,000	1,829	1,581	248		8.0	8.5	-0.5		

CASE 5—A Greek man, aged 20, was admitted to the hospital, July 3, 1923, complaining of swelling of the legs. About six weeks earlier he began to develop anorexia, general weakness and some epigastric discomfort. Two weeks before he entered the hospital his arms, hands, face and abdomen began to swell without any pain. For a day or two before admission he vomited several times, had slight epistaxis once and noticed some pain in his toes. The past and family histories were entirely unimportant.

At the time of admission the temperature was 97 degrees F, the pulse 78 and the respirations normal in rate and character. The face, arms and trunk appeared puffy and there was distinct pitting edema of the ankles and legs and over the sacrum. The skin and the mucous membranes were pale. The submaxillary lymph nodes were slightly enlarged. The lungs were clear. The heart seemed slightly enlarged to the left, a systolic murmur was heard over the apex and the midcardiac area. The systolic blood pressure was 160, the diastolic 90. The abdomen presented signs of moderate ascites. The liver and spleen were not palpable. Ophthalmoscopic examination revealed no evidences of albuminuric retinitis.

The urine contained large amounts of albumin, many red blood cells and granular and cellular casts. Urine cultures on four occasions, July 4, 7, 10 and August 9, yielded *Staphylococcus albus* and nonhemolytic streptococci. He

had a moderate anemia the blood count showed 3,600,000 red blood cells, 65 per cent hemoglobin, and 8,800 leukocytes, with 68 per cent polymorphonuclear neutrophils. A blood culture proved sterile, the Wassermann reaction was negative. Roentgen-ray examination of the heart and lungs revealed no significant abnormalities. Phenolsulphonephthalein excretion, July 7, amounted to 55 per cent in two hours and ten minutes.

He was given a diet containing 50 gm of protein and 2,500 calories, with fluids limited to 1,500 cc a day. July 8, because the edema had not diminished the diet was made salt poor. Under this regimen no improvement was noted. Because he exhibited constantly a negative nitrogen balance the diet was increased July 19 to contain 60 gm of protein and 2,500 calories a day. During the next two weeks the weight diminished gradually from 70.9 to 67.9 kg and the nonprotein nitrogen of the blood, which had been 82 mg per cent July 5, 92 mg, July 10, and 69, July 17, fell to 41, July 20. The blood pressure also fell gradually. August 3, the systolic pressure was 136, the diastolic 74. About the

TABLE 7—Data in Case 5

Date, July	Food Calories	Fluids			Weight, Kg	Total Nitrogen			Urine Non- protein Nitro- gen, Gm	Protein Lost as Albu- min, Gm	Urine Chlo- ride as Sodium Chlo- ride, Gm	Blood Non- protein Nitro- gen, Mg per 100 Cc
		In- take, Cc	Urine, Cc	Bal- ance, Cc		In take, Gm	Urine, Gm	Bal- ance, Gm				
10	2,500	1,550	1,100	450	69.2	8.0	11.2	-3.2			13	92
11	2,500	1,500	1,520	-20	69.4	8.0	13.3	-5.3			15	
12	2,500	1,650	960	690	69.2	8.0	10.7	-2.7			0.9	
13	2,500	1,950	1,240	710	69.1	8.0	12.5	-4.5			14	
14	2,500	1,800	1,280	520	69.1	8.0	12.7	-4.7			14	
15	2,500	1,900	1,170	730		8.0	11.3	-3.3			15	69
16	2,500	1,900	1,380	520		8.0	11.9	-3.9			18	
17	2,500	2,000	1,080	920	70.9	8.0	10.4	-2.4	7.3	19.8	14	
18	2,500	1,800	1,520	280	70.3	8.0	13.7	-5.7	10.1	22.4	13	
Total	22,500	15,250	11,250	4,800		72.0	107.7	-35.7			12.6	
Daily aver	2,500	1,694	1,250	533		8.0	12.0	-4.0			14	
August												
17	2,500	1,900	1,850	50	68.7	9.6	7.4	2.2	4.7	16.9	24	38*
18	2,500	1,400	1,800	-400	64.0	9.6	9.5	0.1	6.9	21.7	2.9	
19	2,500	1,800	2,200	-400	62.9	9.6	7.3	2.3	5.4	11.8	3.3	
20	2,500	2,200	1,830	370	62.9	9.6	9.6	0.0	6.3	20.5	3.6	
21	2,500	2,000	2,000	0	62.4	9.6	8.4	1.2	6.1	14.5	5.2	
22	2,500	2,200	2,500	-300	62.4	9.6	10.6	-1.1	7.0	20.0	5.7	31
23	2,500	2,200	2,200	0	62.4	9.6	9.4	0.2	5.9	21.3	4.9	
24	2,500	2,000	2,500	-300	60.6	9.6	9.2	0.4	6.0	19.6	6.1	
25	2,500	2,200	3,200	-1,000	60.9	9.6	9.8	-0.2	6.7	19.8	7.4	
26	2,500	2,000	2,170	-170	59.8	9.6	7.8	1.8	5.1	17.0	5.9	
Total	25,000	19,900	22,250	-2,150		96.0	89.0	6.8	60.3	183.2	47.2	
Daily aver	2,500	1,990	2,225	-215		9.6	8.9	0.7	6.0	18.3	4.7	

* Nonprotein nitrogen of August 12

middle of August the diuresis, which had been progressively diminishing, suddenly increased, and in the last two weeks in the hospital his weight fell from 66.4 to 59.8 kg. The treatment meanwhile had not been changed. At the end of this period the edema had diminished, blood nonprotein nitrogen was only 31 mg per cent, and he felt so well that he refused to remain in the hospital longer. The albuminuria was quite as profuse as it had been at any time and the urine still contained many red blood cells, leukocytes and casts. There were still slight ascites and vestiges of subcutaneous edema. The anemia had not improved. The daily temperature varied considerably during the first part of his course, frequently rising just above the normal level. The daily swings and the frequency of these abnormal elevations diminished somewhat during the latter part of his stay in the hospital.

Metabolism studies in this case are presented in Table 7. They cover only two periods. During the first, nine days, July 10 to 18, inclusive, he received 50 gm of protein and 2,500 calories daily, with minimum salt and fluids varying from 1,500 to 2,000 c c. During the second period of ten days, August 17 to 26, inclusive, he was given a salt poor diet containing 60 gm of protein and 2,500 calories, and about 2,000 c c of fluid a day.

In the first period the nitrogen in the diet amounted to 72 gm, or 8 gm a days, the equivalent of $\frac{8 \times 6.25}{59.8} = 0.84$ gm per kilogram a day, on the basis of his weight at the time he was discharged from the hospital. Corrected for loss in stools the available dietary nitrogen comes to $72 \times 0.9 = 64.8$ gm. During the same period he excreted 107.7 gm, leaving a negative balance of -42.9 gm representing $\frac{42.9 \times 6.25}{9} = 29.8$ gm of protein a day. The protein lost as albuminuria was only determined for the last two days of the period, when it averaged 21 gm a day. The blood nonprotein nitrogen was 92 mg per cent, July 10, and 69, July 16, two days before the study was terminated. The weight increased from 69.2 to 70.3 kg. The nitrogen excretion due to loss of weight and change of blood nonprotein nitrogen came to $(59.8 \times 0.7) (0.92 - 0.69) + 0.9 [0.92 (69.2 - 59.8) - 0.69 (70.3 - 59.8)] = 12.4$ gm. The actual nitrogen loss referable to protein catabolism and albuminuria was, therefore, $107.7 - 12.4$ gm, or 95.3 gm. The corrected nitrogen balance, then, becomes $64.8 - 95.3 = -30.5$ gm, or $\frac{30.5 \times 6.25}{9} = 21.2$ gm of protein a day. This is almost exactly equivalent to the protein lost as albumin on the last two days of the period.

It is evident then, that the administration of 0.84 gm of protein and 42 calories per kilogram was sufficient to cover the requirements of the nitrogen catabolism, but did not suffice to replace the nitrogen lost as albumin in the urine.

During the second period the food nitrogen came to 96 gm, or $\frac{96 \times 6.25}{10 \times 59.8} = 1$ gm of protein per kilogram a day. Corrected for loss in stools, this becomes $96 \times 0.9 = 86.4$ gm. The urinary nitrogen was 89.0 gm, leaving a negative balance of -2.6 gm, or $\frac{2.6 \times 6.25}{10} = 1.6$ gm of protein a day. The protein lost as albumin in the urine was 183.2 gm, or 18.3 gm a day. The urinary nonprotein nitrogen excretion amounted to 60.3 gm. The weight fell from 64.7 to 59.8 kg and the blood nonprotein nitrogen, which had been 38 mg per cent, August 12, was 31 mg, August 27. The actual protein catabolism, therefore, amounted to $60.3 - (59.8 \times 0.7) (0.38 - 0.31) + (64.8 - 59.8) (0.9 \times 0.38) = 55.6$ gm, which is equivalent to $\frac{55.6 \times 6.25}{10} = 34.7$ gm of protein a day, or 0.57 gm per kilogram a day.

At first sight it would appear that the mere addition of 10 gm of protein had resulted in sparing almost double that amount. It is, however, far more probable that improvement in the clinical condition of the patient had been associated with a reduction of the rate of nitrogen catabolism and that this had enabled him to attain nitrogen equilibrium in spite of a profuse albuminuria. One gram of protein and 42 calories per kilogram did not, however, prove sufficient to permit him to repair the effects of previous wastage.

CASE 6—An American man, aged 34, a mechanic, was admitted to the hospital, Oct 5, 1923, because pus and blood had been discovered in the urine.

About a month before admission he had had a sore throat. A week later a peritonsillar abscess was drained. Although the pain and edema of the throat and neck subsided rapidly, he did not recover his strength and suffered from indigestion, vomiting frequently after meals. Two days after the abscess was opened he noticed that urination was painful, that he had to void more often than usual, and that his urine was bloody. All these symptoms persisted until he entered the hospital. The past and family histories were entirely negative.

At the time of admission he appeared well developed and nourished and quite comfortable. His color was good, there were no evidences of edema, and temperature, pulse and respirations were normal. The tonsils were enlarged and red, the scar of the operation was still visible, and the pharynx was congested. The systolic blood pressure was 180, the diastolic 90. Physical examination revealed no other abnormalities.

Ophthalmoscopic examination was negative. October 6, the second day in the hospital, numerous fresh conjunctival hemorrhages appeared. The urine was distinctly smoky, and contained a moderate amount of albumin, many red blood cells and leukocytes and a few granular casts. Culture of the urine recovered nonhemolytic streptococci. The blood Wassermann reaction was negative. Phenolsulphonaphthalein excretion, October 6, was 65 per cent in two hours and ten minutes. The blood nonprotein nitrogen was 49 mg per cent.

TABLE 8—Data in Case 6

Date, Oct	Food, Calories	Fluids			Weight, Kg	Total Nitrogen			Urine Protein Non- protein Nitro- gen, Gm	Blood Protein Lost as Albu- min, Gm	Non- Nitro- gen, Mg per 100 C c	Plasma Pro- tein, per cent
		In take, C c	Urine, C c	Bal- ance, C c		In take, Gm	Urine, Gm	Bal- ance, Gm				
7	2,500	3,200	1,226	980	71.0	80	75	05	65	58	49	7.55
8	2,500	2,800	1,980	820		80	110	-30	92	108		
9	2,500	3,800	1,480	2,320		80	91	-11	81	60		
10	2,500	3,000	1,940	2,060		80	105	-25	101	26		
11	2,500	3,600	2,400	1,200		80	105	-25	100	28		
12	2,500	4,000	2,030	1,970		80	79	01	72	39		
13	2,500	3,800	2,200	1,600		80	89	-09	85	28		
14	2,500	3,200	1,920	1,280		80	74	06	71	21		
15	2,500	4,000	3,020	980	69.2	80	90	-10	83	44	37	
Total	22,500	31,400	18,190	13,210		720	817	-110	751	412		
Daily aver	2,500	3,489	2,021	1,468		80	91	-12	84	46		

He was given a diet containing 50 gm of protein, 2,500 calories and large amounts of fluid. With this treatment the urinary changes diminished, the blood nonprotein nitrogen and the blood pressure both fell, and his subjective symptoms rapidly improved. At the end of ten days the urine contained little albumin, moderate numbers of red blood cells and a few leukocytes. Because he had exhibited a negative nitrogen balance the dietary protein was increased to 60 gm, October 16. Improvement continued.

October 26, adenoidectomy and tonsillectomy were performed. There was an immediate but temporary aggravation of the urinary picture followed by an uneventful recovery. At the time of his discharge from the hospital, November 9, the urine contained only a trace of albumin and an occasional red blood cell. The systolic blood pressure was 110, the diastolic 70. The phenolsulphonaphthalein excretion was 80 per cent in two hours and 10 minutes.

Except during the first day in the hospital and the forty-eight hours immediately after operation, the temperature remained normal throughout his stay. At the time of admission he had a moderate anemia, 3,900,000 red blood cells with 65 per cent hemoglobin. This condition was improving when he left, the red cells having risen to 4,500,000 and the hemoglobin to 75 per cent. Metabolism studies appear in Table 8.

Metabolism studies in this case were quite incomplete because urine collections were unsatisfactory. It is, however, possible to draw some conclusions from the first period of nine days, October 7 to 15, inclusive. During this period he received 72 gm of nitrogen in the diet or, correcting for loss in stools, 65 gm of available nitrogen, and excreted in the urine 82 gm, leaving a negative balance of 17 gm, representing $\frac{17 \times 6.25}{9} = 11.8$ gm of protein a day. During the same period he lost as albumin in the urine 41 gm of protein, or 46 gm a day. The administration, therefore, of 0.71 gm of protein and 36 calories per kilogram a day did not suffice to prevent nitrogen wastage. The urinary nonprotein nitrogen was 75 gm. This must be corrected for a loss of weight from 71 to 69.2 kg and reduction of the blood nonprotein nitrogen from 49 mg per cent to 37. In this case there was no edema and the loss of weight is presumably referable to actual tissue wastage. The nitrogen catabolism, therefore, amounts to $75 - (71 \times 0.7 \times 0.49) - (69.2 \times 0.7 \times 0.37) = 69$ gm. This represents $\frac{69 \times 6.25}{9} = 47.9$ gm of protein per day, or 0.68 gm per kilogram a day. In view of the probability that urine collections were incomplete, this must be considered as a minimal value.

In this case, during the acute stage of the disease, the administration of 0.71 gm of protein and 36 calories per kilogram a day was not enough to prevent nitrogen wastage. The loss in this instance cannot be ascribed entirely to the albuminuria, which was relatively slight. The subsequent course does not permit an evaluation of the effect of altering the diet. Apparently, he attained equilibrium and a positive nitrogen balance as soon as the diet was increased. Even if it is assumed that the urine collections were complete, the clinical condition and albuminuria improved so considerably at the same time that the metabolic alteration cannot be attributed to the dietetic changes alone.

COMMENT

From these studies certain general conclusions can be drawn. In the first place it is quite evident that by the proper regulation of diet it is possible to replace nitrogen lost as albumin. This cannot, however, be effected unless allowance is specifically made for such loss. The use of comparatively high caloric diets with a considerable excess of fat and carbohydrate in this, as in other conditions, results in the reduction of the nitrogen metabolism. By means of such high caloric diets the protein catabolism, as measured by the nonprotein nitrogen output, reaches levels quite as low as, but no lower than, those reported in other conditions, from 0.5 to 0.7 gm per kilogram a day. Over and above this minimum a sufficient excess of protein must be given to replace albuminuric nitrogen.

Most of these patients, when they are given an adequate excess, exhibit a tendency to store large amounts of protein over considerable periods, in one case for almost three months. This is probably evidence that they have undergone protein starvation during the preceding period. It is quite impossible to say how much of this has been due to mis-

directed dietetic treatment and how much to the fact that the disease itself is associated with an augmented nitrogen metabolism. Some of the patients had received little or no dietary treatment before they came to the hospital so that restriction of diet probably played only a minor part in the production of the protein wastage. The wasting character of the disease has been too little stressed in earlier studies. Emaciation was evident in this series in every instance when the disease had lasted more than a short time. It became obvious, however, only after the edema had disappeared. The latter lends to most of the patients a specious appearance of being well nourished.

The administration of protein in excess of that required to meet the needs of nitrogen catabolism and replacement of the protein lost as albumin in the urine results in the storage of nitrogen. This presumably goes to the restoration of depleted tissue protein. Increasing the protein in one case to 75 gm from 60 gm resulted in the storage of almost the entire additional protein. How far this process could be continued to advantage it is impossible to tell. It is highly improbable that a true high protein diet limited in fat or carbohydrate or both would be relatively as effective. Adequate fat and carbohydrate are essential factors in the production of low nitrogen catabolism. A large part of the success obtained has been due to the fact that the nitrogen catabolism was reduced to a low level, thus releasing as much protein as possible for other purposes.

The general practice of using total nitrogen excretion as a measure of nitrogen metabolism cannot be applied to nephritic studies. Nitrogen lost as albumin in the urine has obviously played no useful part in the metabolic processes of the body. If this is not taken into consideration the nitrogen metabolism is likely to be exaggerated. In estimating the true protein catabolism, changes in the weight of the subject and in the level of the blood and tissue nonprotein nitrogen must also be taken into consideration. A positive nitrogen balance cannot be interpreted as evidence of inability on the part of the kidney to excrete protein waste products, nor is a negative balance a sign that the individual is overcoming the effects of such a retention. This has already been brought out by Mosenthal and Richards³ and others. The nitrogen balance and the level of the blood nonprotein nitrogen are only indirectly dependent on the amount of protein in the diet and are only partly determined by the functional state of the kidney. The rate of nitrogenous metabolism in these cases appears to be the chief determinant of the level of blood nonprotein nitrogen. The latter has been elevated only in periods when the metabolism was relatively high and usually when there was a negative nitrogen balance. Increasing dietary protein can then be expected to raise the nonprotein nitrogen of the blood only if it raises the protein

metabolism of the body When such an increase contributes only to the restoration of depleted tissue, it has no such effect

In all but one of the cases discussed above the blood nonprotein nitrogen was elevated during the early part of the course, falling to the normal level as the disease improved Many factors probably contribute to the production of the azotemia Although the ability of the organism to concentrate metabolites in the urine is relatively unimpaired in most instances, this impairment is rendered more serious by reason of the associated oliguria In addition to these factors, however, a relatively large nitrogen catabolism usually plays an important rôle When the latter has ceased the azotemia has disappeared even when the urine volume remained scanty It is important to ascertain the underlying cause of this high protein metabolism as a guide to the treatment of the more acute stages of nephritis It is easy to ascribe the observed reductions of metabolism to effective dietetic therapy They may quite as well have been due to variations in the course of the disease itself Whether the high nitrogen catabolism of the acute stages can be controlled is as yet undetermined It is reasonably certain that it can be favorably influenced by measures similar to those which have been employed in these cases The few patients in our series who have progressed unfavorably have presented complicating conditions that have made metabolism studies impossible or unintelligible

That the stage of the disease may be the predominant factor in determining the nonprotein nitrogen is suggested by some studies on the effect of urea administration in Case 2 After improvement had set in urea was given to this patient in an attempt to hasten diuresis In this respect it was comparatively ineffectual but it did not provoke an azotemia Although the amounts of urea administered were smaller than those advocated by McLean, they were sufficient to raise the nonprotein nitrogen output well above the level at which, at an earlier stage, he had shown definite azotemia From this one cannot argue that his ability to excrete nitrogen was normal, there was a certain delay in the excretion of the urea that has not been observed in normal persons His powers of compensation were, however, not overtaxed and he was quite able to take care of the load of added urea without significant alteration of the blood nitrogen

In all the cases here presented, with a possible single exception, the disease had an infectious origin, or at least began immediately after a definite infection The urines, at least in the acute stages, contained red blood cells and leukocytes in varying numbers as well as albumin and casts During the same stages blood pressure and nonprotein nitrogen were also somewhat elevated With the one exception noted above Case 3 none of them could have been admitted into the group which

Muller,¹⁰ Epstein,⁴ and Vollhard and Fahl¹ have called nephrosis. At the same time they present many of the phenomena characteristic of this condition—the tendency to edema, profuse albuminuria, and especially reduction of plasma proteins. Case 3 gives the typical history and clinical signs of nephrosis. The disease in his case developed insidiously and, while he was under observation, blood pressure and nonprotein nitrogen were never elevated and hematuria was not observed.

At first sight there seems to be a real difference between the two types of cases. On closer analysis, however, the distinction becomes less convincing. In all the "infectious" cases, as the acute stage of the disease subsides hematuria, hypertension and azotemia diminish. Sometimes this leads to the production of a condition, as for example in the latter stages of the hospital course of Case 2, that is entirely indistinguishable from that of nephrosis. Granted that the two are separate entities, clinical differentiation is exceedingly difficult if hematuria, hypertension and azotemia are the only distinguishing features, because the latter are not persistent in cases that have an admitted nephritis. It is not inconceivable that "nephrosis" is only a more or less quiescent stage of a nephritic process and that the "insidious onset," which is so much emphasized, masked the symptoms of an acute stage. It has been long recognized and is apparent from these studies that nephritis seldom develops during the acute stages of the infection that causes it, but usually begins during convalescence from the primary disease. For this reason connection with the etiologic factor is often overlooked. Certainly differential diagnosis of the two conditions is impossible from a clinical standpoint except after prolonged observation.

Epstein¹¹ asserts that the basal metabolism of true nephrosis cases is regularly low. Both he and Eppinger¹² advocate thyroid treatment for this reason. A few basal metabolism determinations were made in this series but showed no consistent changes, they varied from +16 to -16 per cent. In the one typical nephrosis case values of +16 and -5 per cent were obtained. These alterations are of doubtful significance. It is possible that Epstein's low figures and our own are merely another expression of the undernutrition exhibited in the nitrogen metabolism. Two cases (Cases 3 and 4) had more than one determination. In both instances the second, made when the condition of the

10 Muller, Friedrich. *Bezeichnung und Begriffsbestimmung auf dem Gebiete der Nierenkrankheiten*, 1917.

11 Epstein, A. A. Further Observations on the Nature and Treatment of Chronic Nephrosis, *Am J M Sc* **163** 167 (Feb.) 1922.

12 Eppinger, Hans. *Zur Pathologie und Therapie des menschlichen Odems zugleich ein Beitrag zur Lehre von der Schilddrüsenfunktion*, Eine klinisch experimentelle Studie, Berlin, 1917.

patient was improved, was the lower, conforming to the nitrogen metabolism changes

In two cases tonsillectomy was performed in order to remove the infection that had provoked the nephritis. In both instances favorable end-results were obtained, although in one there was an immediate exacerbation of the nephritis. In another case tonsillectomy proved entirely ineffectual. It is important to note that in this last case the operation had quite as little effect in preventing respiratory infections. Throughout his stay in the hospital Patient 1 had recurrent exacerbations of hematuria, attended in each case with mild sore throat, coryza and temperature. Concerning the mechanism that connects the infections with the nephritis only speculation is possible. One gains the impression from this case and others that there is some connection between the two in certain cases and that anything that tends to prevent infections will also check the progress of the renal disease. When tonsillectomy has such an effect it may be a beneficial procedure. The indiscriminate removal of suspected organs is not, however, advisable nor likely to have any favorable effect.

In every case except one (Case 1) in which the urine was cultured, organisms were recovered, usually nonhemolytic streptococci. This cannot be accepted as definite evidence that these cocci were the cause of the infection because of the notorious difficulty of obtaining urine free from contaminating bacteria. The probability that the organisms actually came from the deeper portions of the urinary tract is somewhat increased in those cases in which they were obtained on several occasions. In all instances the urine was collected in a series of tubes and only those cultures are reported as positive in which the same organism was recovered from all tubes, usually in both smear and culture. If these bacteria are to be accepted as the etiologic agents of the nephritis one must postulate some kind of a diffuse, sluggish infectious process of hematogenous origin in which the organisms are established in the renal tissue, a condition that pathologists rarely encounter. In this case it is hard to see how removal of the original focus of infection in the tonsils can benefit the condition.

The fact that nephritis seldom develops until the primary infectious process is subsiding also argues against a direct infection of the kidney unless it is presumed that the renal lesion begins during the more acute stages of the infection but requires a certain period to develop to the point of producing symptoms. How further exacerbations or recurrences of the original remote focus may affect the kidney lesion is also obscure. Until some of these questions are answered, however, treatment directed toward the cure of the disease can have no rational basis.

Discussion of the changes in plasma proteins, electrolytes, diuresis and water balance will be reserved for subsequent articles.

SUMMARY AND CONCLUSIONS

A study of the nitrogen metabolism of certain patients with acute and chronic parenchymatous nephritis has been made in an attempt to determine to what extent protein lost as albumin in the urine can be replaced by food protein

1 The total urinary nitrogen of these patients is not a satisfactory measure of nitrogen catabolism

2 The nitrogen catabolism can only be estimated from the urinary nonprotein nitrogen after proper allowance has been made for changes in blood and tissue nonprotein nitrogen and variations of body weight due to diuresis or accumulation of edema

3. By the administration of large amounts of carbohydrate and fat it has proved possible to reduce the protein catabolism to from 0.5 to 0.7 gm per kilogram a day

4 If enough protein is given to cover the nitrogen catabolism plus an additional amount equivalent to that lost as albumin in the urine, nitrogen wastage may be prevented

5 Most of these patients when they enter the hospital show evidences of previous protein deficiency. If they are given more than enough protein to replace the amount lost in the urine, they will store the excess within certain limits, thus repairing the effects of previous nitrogen wastage

6 This protein wastage may be partly due to early dietary mismanagement. The loss of protein as albumin in the urine is certainly a serious contributory cause. It also seems probable that the disease itself, in its more acute stages at least, is characterized by a higher protein metabolism than normal. This is suggested by the results of these studies

7 Abnormally high blood nonprotein nitrogen has only been observed when the nitrogen catabolism was relatively high and has usually returned to the normal level as the clinical condition of the patient improved and the nitrogen catabolism diminished

METHODS AND RESULTS OF OXYGEN TREATMENT IN PNEUMONIA *

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The object of this investigation is to secure further information concerning the importance of oxygen as a therapeutic agent. In the first part of the paper, evidence will be presented bearing on the effectiveness of certain methods of administering oxygen, in the second part, a report will be made of the results of oxygen treatment by the more desirable of these methods.

Pharmacologic experience demonstrates that the therapeutic activity of a drug is closely related to the dosage employed. Such a conception, however, has had very little application to the therapeutic use of oxygen. Inefficient methods of administration and the absence of any precise knowledge as to how much oxygen the patient actually receives appear to be important factors accounting for the confusion surrounding the subject. It seems of value to define the limitations of a few commonly used methods and to inquire into the qualifications of an effective method, for it is obvious that any final judgment of the importance of oxygen as a therapeutic agent must be postponed until the factor of dosage is adequately considered.

In recent years the introduction of adequate methods, the recognition of oxygen deficiency in the arterial blood in patients with pneumonia and several controlled reports of effective treatment have led to a decidedly more favorable opinion than was previously held. However, the compiled results of controlled oxygen treatment in pneumonia are based on fewer than fifty cases¹. In this article the clinical and laboratory data of sixteen additional cases will be discussed. The theoretical basis of oxygen therapy and the indications for its use have been considered elsewhere².

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1 Meakins, J. C. The Therapeutic Value of Oxygen in Pulmonary Lesions, *Brit. M. J.* **1** 324 (March 6) 1920, Observations on the Gases in Human Arterial Blood in Certain Pathological Conditions and Their Treatment with Oxygen, *J. Path. & Bacteriol.* **24** 79 (Jan.) 1921. Means, J. H., and Barach, A. L. The Symptomatic Treatment of Pneumonia, *J. A. M. A.* **77** 1217 (Oct. 15) 1921. Barach, A. L., and Woodwell, M. N. Studies in Oxygen Therapy, II, In Pneumonia and Its Complications, *Arch. Int. Med.* **28** 394 (Oct.) 1921. Stadie, W. C. The Treatment of Anoxemia in Pneumonia in Oxygen Chamber, *J. Exper. Med.* **35** 337 (March) 1922. Hastings, A. B., Neill, J. M., Morgan, H. J., and Binger, C. A. L. Blood Reaction and Blood Gases in Pneumonia, *J. Clin. Invest.* **1** 25, 1924.

2 Barach, A. L. The Therapeutic Use of Oxygen, *J. A. M. A.* **79** 693 (Aug. 26) 1922. Means, J. H. Dyspnea, *Medicine* **3** 309 (Aug.) 1924.

The effective administration of oxygen apparently began in the year 1917 when the Haldane apparatus was used in the treatment of acute pulmonary edema of war gas poisoning.³ During the same year Meltzer⁴ reported the successful use of the oral insufflation apparatus. In 1921 Barach and Woodwell⁵ described a rebreathing apparatus for cases of pneumonia and cardiac insufficiency. Henderson⁶ in 1922 described an apparatus employed in resuscitation from gas poisoning and suggested its use in pneumonia. Since 1921 oxygen chambers have been used by Barcroft⁷ and Poulton⁸ in England and by Stadie⁹ and Binger¹⁰ in this country. A bed tent was described by Hill,¹¹ a head tent by Roth¹² and recently a portable oxygen tent by Barach and Binger¹³. The nasal catheter was introduced during the war and has been widely used since then. The oldest and still the most common method is the administration of oxygen by a funnel held in front of the patient's face. The administration of oxygen intravenously, subcutaneously or by rectum will not be considered as these methods seem to have little theoretic basis. Ordinarily, the inspired air contains approximately 21 per cent oxygen. The methods that have been used vary so widely that the inspired air may contain anywhere from 21 to 100 per cent oxygen. It is probable that oxygen to be of therapeutic potency should be administered at a certain optimal concentration and within a certain maximal and minimal range.

3 Haldane, J. S. Therapeutic Administration of Oxygen, *Brit M J* **1** 181 (Feb 10) 1917

4 Meltzer, S. J. Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, *J A M A* **69** 1150 (Oct 6) 1917

5 Barach, A. L., and Woodwell, M. N. Studies in Oxygen Therapy, I, In Cardiac Insufficiency and Related Conditions, *Arch Int Med* **28** 367 (Oct) 1921. Barach, A. L. A Simple Apparatus for Administering Oxygen, *J A M A* **78** 334 (Feb 4) 1922

6 Henderson, Yandell, and Haggard, H. W. Report 1 of Commission of Resuscitation from Carbon Monoxid Asphyxia to American Gas Association, *J A M A* **79** 1137 (Sept 30) 1922

7 Barcroft J. H., Hunt, G. H., and Dufton, D. The Treatment of Chronic Cases of Gas Poisoning by Continuous Oxygen Administration in Chambers, *Quart J Med* **13** 179 (Jan) 1920

8 Campbell, J. M. H., Hunt, G. H., and Poulton, E. P. An Examination of the Blood Gases and Respiration in Disease, *J Path & Bacteriol* **26** 234 (April) 1923

9 Stadie (Footnote 1, fourth reference)

10 Binger, C. A. L. The Construction and Management of an Oxygen Chamber, *Mod Hosp* **24** 186 (Feb) 1925

11 Hill, Leonard. A Simple Oxygen Bed Tent and Its Use in a Case of Edema and Chronic Ulcer of the Leg, *J Physiol* **50**, May 24, 1921, *Proc Physiol Soc*, p 20

12 Roth, Paul. Improved Apparatus for the Therapeutic Administration of Oxygen, *Mod Hosp* **22** 404 (April) 1924

13 Barach, A. L., and Binger, C. A. L. A Portable Oxygen Tent, *J A. M A* **85** 190 (July 18) 1925

We have come to the conclusion that the inspired air should contain between 30 and 60 per cent oxygen before oxygen administration can be definitely considered a therapeutic agent, and that for most cases 40 per cent seems optimal. The maximum concentration at which oxygen may be administered with safety is 70 per cent. When animals are exposed to air mixtures containing more than 70 per cent oxygen for from one to four days death may ensue as a result of an acute serous pneumonia¹⁴. Air mixtures of 70 per cent oxygen are said to be without danger for this period of time. We have kept animals in an oxygen chamber containing 60 per cent oxygen for periods as long as six months without harmful effects¹⁵. It seems advisable therefore to administer oxygen continuously in concentrations not exceeding 60 per cent. In our experience the majority of pneumonia patients with oxygen deficiency recorded in their arterial blood are restored to or near the normal value by breathing air containing 40 per cent oxygen. Although clinical and laboratory data indicate that 30 per cent oxygen may register some improvement in the mild and occasionally in the severe cases of arterial anoxemia, the majority of cases are not much improved until from 40 to 50 per cent of oxygen is administered. A method, then, that is capable of providing 40 per cent or more oxygen may be ranked as effective, one that provides 30 per cent oxygen as slightly effective, and one that provides less than 30 per cent as relatively ineffective.

The cause of arterial anoxemia in pneumonia depends on the type of lung involvement. If a blood flow is present through consolidated lung, as may happen in the early stage of the disease, even the highest concentration of oxygen will be unable to make up for the deficiency created by unventilated blood entering the aortic stream, a circumstance that is explained by the oxygen absorption curve of hemoglobin. Edema and congestion of alveolar walls appear to be more common factors, with possible additional influences, such as shallow breathing and altered pulmonary diffusion. Under these conditions increased concentrations of oxygen penetrate the alveolar wall and overcome the arterial anoxemia. The theoretical aspects of this subject have recently been clearly presented by Lundsgaard and Van Slyke¹⁶.

14 Smith, J. L. The Pathological Effects Due to Increase of Oxygen Tension in the Air Breathed, *J. Physiol.* **24** 19, 1899. Karsner, H. T. The Pathological Effects of Atmosphere Rich in Oxygen, *J. Exper. Med.* **23** 149 (Feb.) 1916.

15 Barach, A. L. The Effect of the Inhalation of Oxygen over Long Periods of Time on Normal Rabbits and Rabbits with Pulmonary Tuberculosis, to be published.

16 Lundsgaard, Christian, and Van Slyke, D. D. Cyanosis, *Medicine* **2** 1 (Feb.) 1923.

METHODS

The two methods first investigated were the tube and funnel and the nasal catheter. In each case samplings of air were taken from the nasopharynx during the administration of oxygen. A small tube or catheter was passed into the nasopharynx, and the projecting end directly connected with the simplified oxygen analyzer described by Binger¹⁰. In this method the maximum error is 0.5 per cent, an accuracy sufficient for the purpose. A gauge especially calibrated to deliver oxygen in liters per minute was used in conjunction with high pressure oxygen tanks. In sampling the nasopharyngeal air it was not possible to obtain inspired fractions separate from expiratory fractions, so that a mixture was commonly obtained from both phases, both in the patients with pneumonia and in the normal subject tested. This gives a reading of approximately 19.5 per cent for the nasopharyngeal air, instead of 21 per cent for the air inspired.

1 *Tube and Funnel*—In this method, oxygen is bubbled through a water bottle, from which it is conducted by a rubber tube to a glass funnel held in front of the patient's nose and mouth. The distance from the face as well as the amount of oxygen bubbled through the bottle varies widely. In the following experiments the funnel was held one-half inch (1.27 cm) from the nose and oxygen run from the tank at (1) 0.5 liter per minute, (2) 1 liter, equivalent to fairly vigorous bubbling, and (3) 2 liters per minute. The results are seen in Table 1.

TABLE 1—*Effect of Administration of Oxygen Through Funnel on Oxygen Concentration of Nasopharyngeal Air in Patient with Pneumonia*

Oxygen Flow Through Funnel, Liters per Minute	Respiratory Rate per Minute	Oxygen Concentration of Nasopharynx, per Cent
None	48	19.0
0.5	48	20.0
1.0	48	20.5
2.0	48	22.0

It is seen that the nasopharyngeal air may be practically unchanged or at the maximum may contain 22 per cent oxygen, indicating approximately 24 per cent oxygen in the inspired air. No change in cyanosis or breathing was manifest. These results confirm the clinical impression that the funnel method is practically useless.

2 *Nasal Catheter*—The nasal catheter is said to have been introduced by Captain Stokes¹⁷ during the war for treatment of the acute pulmonary edema caused by gas poisoning. It was often used in place of the Haldane apparatus, in which a mask was applied to the patient's face. The comments of the men who used both methods are of interest. Douglas¹⁷ found the Haldane apparatus very effective and the nasal

¹⁷ Stokes. Discussion on Therapeutic Use of Oxygen, Proc Roy Soc Med (Sect Therap and Pharmacol) 13: 59, 1920.

catheter less effective Cummins¹⁷ found it difficult to use the mask because of the discomfort it provoked Ryle¹⁷ used the nasal catheter with fairly good results Masks were improvised at his station but were not tolerated by the men Hamil¹⁷ considered the nasal tube satisfactory but wasteful and also found the mask badly tolerated, especially in warm climates Hoover¹⁸ said that the gassed men begged to be relieved of the mask and preferred to have the oxygen conducted by a soft rubber tube in their nostrils, though by the latter method he did not see a single case in which the cyanosis was diminished Similar differences in opinion are found in clinics where the nasal catheter has since been used

The foregoing differences seem to be due in part to the variable effectiveness of the catheter method In the first place the catheter may be placed in the anterior nares, or be plugged by nasal secretions, or have only one opening at the end, which may be closed by contact with the nasal mucous membrane The rate at which oxygen is bubbled through the water bottle is another variable factor In our observation it was often 0.5 liter per minute and occasionally 1 liter per minute With the low pressure tanks in universal use oxygen begun at 1 liter per minute in one hour falls to 0.5 liter per minute unless readjusted

It is possible to calculate the degree of oxygen enrichment that the nasal catheter may furnish from the tidal air, the respiratory rate and the oxygen administered in liters per minute (Table 2 for data on pneumonia patients with different pulmonary ventilation under varying conditions of oxygen flow) For example, if 1,000 c.c. of oxygen per minute is run into the nasopharynx the amount inhaled is the portion that runs in during inspiration, the exhaled air obviously containing the oxygen run in during expiration If the rate of respiration is 40 per minute, the oxygen added to each inspiration is $\frac{1}{2}$ by $\frac{1}{40}$ by 1,000 c.c., or 12.5 c.c. If the tidal volume is 300 c.c., the oxygen content of the inhaled air is $63 + 12.5$, or 75.5 c.c., or 25.2 per cent of the inspired air Thus, when the nasal catheter is used with oxygen bubbling fairly vigorously, the oxygen concentration of the inspired air is 25.2 per cent If oxygen is admitted at the rate of 2,000 c.c. per minute, a large amount for a nasal catheter, the oxygen percentage of the inspired air is in this instance 30.6 per cent¹⁹

18 Hoover, C. F. Oxygen Therapy, J. A. M. A. 71:880 (Sept. 14) 1918

19 Inspiration is generally shorter than expiration, the time kept by the two phases being in the proportion 10:12. The pause between two respirations lasts from about one-third to one-fifth of the total time between the beginning of one inspiration and the next (Schafer's Physiology 11:281). Vierordt (Anatomische, Physiologische und Physikalische Daten und Tabellen, p. 258) gives the time for the total respiratory excursion as from 3 to 3.8 seconds, and the ratios of inspiration and expiration variously as 8:12, 10:12, 9:13. In respiratory disease expiration may be further lengthened. For purposes of approximate calculation of the amount of oxygen admitted during inspiration we have chosen a 1:1 ratio.

TABLE 2—*Effect of Administration of Oxygen Through Nasal Catheter on Oxygen Concentration of Inspired Air Calculated for Pneumonia Patients Under Varying Conditions of Oxygen Flow*

Oxygen Flow Through Catheter, Liters per Minute	Respiratory Rate per Minute	Tidal Volume, Cc per Inspiration	Duration of Inspiration, Minutes	Oxygen Added per Inspiration, Cc	Oxygen of Inspired Air, per Cent
None	40	250	0.012		21.0
500	40	250	0.012	6.0	23.4
1,000	40	250	0.012	12.0	25.8
2,000	40	250	0.012	24.0	30.6
500	50	250	0.010	5.0	23.0
1,000	50	250	0.010	10.0	25.0
2,000	50	250	0.010	20.0	29.0
500	40	200	0.012	6.0	24.0
1,000	40	200	0.012	12.0	27.0
2,000	40	200	0.012	24.0	33.0

That this method of reasoning is approximately correct may be seen by reference to Table 3, which gives data obtained from a patient with pneumonia. It is seen that the nasopharyngeal air contained 22 per cent oxygen when 500 c c of oxygen was administered, 25 per cent when 1,000 c c of oxygen was administered, and 30 per cent when 2,000 c c of oxygen was the rate of flow through the catheter.

TABLE 3—*Effect of Administration of Oxygen Through Nasal Catheter on Oxygen Concentration of Nasopharyngeal Air in Patient with Pneumonia*

Oxygen Flow Through Funnel, Liters per Minute	Respiratory Rate per Minute	Oxygen Concentration of Nasopharynx, per Cent
None	48	19.0
0.5	48	22.0
1.0	48	25.0
2.0	48	30.0

If oxygen is administered to a subject with an intact respiratory apparatus, more oxygen is added per inspiration, but the increased tidal air partially counterbalances this effect, thus keeping the concentration of oxygen in the air breathed at similar low levels. An experiment was performed on a control subject who attempted to breathe approximately the character of pulmonary ventilation found in normal respiration and in pneumonia. The results are seen in Table 4.

The calculated results are slightly higher than those actually obtained, owing to the admixture of expiratory fractions in the latter. They confirm previous calculations and results on pneumonia patients, namely, that the concentration of oxygen in the inspired air may vary between 22 and 35 per cent, depending on the rate of flow. When 1 liter a minute is the amount administered, the concentration of oxygen in the inspired air through the use of the nasal catheter is from 25 to 27 per cent.

One exception to these conclusions must be emphasized. If the oxygen is administered by nasal catheter in a patient who breathes

through his mouth the inspired air may not be enriched but consists mostly of room air. The oxygen passes in and out of the nose, gradually elevating the oxygen concentration of the nasopharynx, whereas the pharynx through which respiration is being accomplished may contain only 21 per cent oxygen. This may be an added factor accounting for the discrepancy in the results of catheter oxygen treatment.

If oxygen is bubbled at the vigorous rate of 2 liters a minute, the pneumonia patient may receive approximately 30 per cent oxygen, which places this method in the slightly effective classification. In order to accomplish this degree of effectiveness the following points have been found helpful:

TABLE 4—*Effects of Administration of Oxygen Through Nasal Catheter on Oxygen Concentration of Inspired Air of Normal Individual (1) Calculated for Quiet Breathing and for Induced Dyspnea, (2) Actually Obtained in Nasopharynx*

Oxygen Flow Through Catheter, Liters per Minute	Respiratory Rate per Minute	Tidal Volume, Cc per Inspiration	Duration of Inspiration, Minutes	Oxygen Added per Inspiration, Cc	Calculated Oxygen of Inspired Air, per Cent	Obtained Oxygen of Nasopharynx, per Cent *
None	18	500	0.0278		21.0	19.5
0.5	18	500	0.0278	13.9	23.8	22.0
1.0	18	500	0.0278	27.8	26.5	25.0
2.0	18	500	0.0278	55.6	32.1	30.0
0.5	40	250	0.012	6.0	23.4	21.5
1.0	40	250	0.012	12.0	25.8	25.0
2.0	40	250	0.012	24.0	30.6	29.0

* These figures represent mixtures of inspired and expired air, and are, therefore, apt to be lower than the inspired air by from 1 to 2 per cent.

1 A catheter of small diameter, such as a No. 10 F, is to be preferred because the larger sizes are more uncomfortable and more apt to cause mouth breathing.

2 It is advisable to have four holes placed within the terminal 1 inch (2.5 cm) of the catheter as clogging is less apt to take place, and as the high rate of flow is better tolerated than when one hole is present. In the latter instance a vigorous stream of oxygen directed against the nasopharynx causes a painful burning sensation.

3 The catheter should be cleaned at least every four hours.

4 It should be put in place, preferably by a physician, by passing it along the inferior surface of the nasal cavity until it strikes the posterior surface of the nasopharynx, then it should be withdrawn one-half inch (1.27 cm), passed over the forehead and fastened there with adhesive.

5 When 2 liters a minute causes an uncomfortable sensation, two catheters should be used with a connecting Y tube. Some patients, however, complain of suffocation with two catheters, others institute mouth breathing, and with them one catheter must be employed.

6 High pressure oxygen tanks seem the best way to employ this kind of therapy with any assurance of a constant rate of flow. The low pressure tanks cannot be regulated at a given flow because the diminishing pressure results in a gradually lessening output. They are not equipped with a gage. Furthermore, the expense of low pressure tanks is almost prohibitive if 2 liters of oxygen per minute is prescribed.

This aspect of the question is of importance both from the standpoint of the hospital and that of private patients, and warrants further consideration.

At 2 liters a minute the oxygen consumed in twenty-four hours is 2,880 liters, or 103 cu ft. There are in general three common low pressure tanks available, large, medium and small size. In the medium size the charge to the hospital is 87 cents a cu ft, or approximately \$9 for one day's treatment to one person, and \$63 for one week. For the small size the charge is 13.5 cents a cu ft, or approximately \$14 for one day and \$100 for one week. With high pressure oxygen either in the large or small size tanks the charge is 1.55 cents a cu ft, or \$1.60 a day and \$11.20 for one week. In outside private practice, the cost of low pressure oxygen tanks may be three or four times as much, whereas high pressure oxygen costs only one-half again as much as the hospital charge. Furthermore, a large low pressure tank would have to be changed four times in twenty-four hours, a medium size tank eight times, a small low pressure tank ten times, and a small high pressure tank only once. A large high pressure tank at the same rate of flow, i. e., 2 liters per minute, lasts more than two days.

The disadvantages of the high pressure oxygen tank are the increased weight and the fact that a reducing valve has to be attached to the tank before it is used. We have employed rubber wheeled trucks for the large and small high pressure tanks, these make them easy to move from ward to ward by nurse or orderly. With all types of high pressure oxygen tanks care in adjustment of the reducing valve is necessary to prevent accidents.

3 *Haldane Method*—This method has the advantage of an approximate regulation of the concentration of oxygen administered. In our hands the use of a face mask limits its application largely to comatose or apathetic patients because of the feeling of suffocation it engenders. The Henderson apparatus carries a little further the regulation of the oxygen concentration of the air breathed but likewise utilizes a face mask.

4 *Rebreathing Apparatus*—In this method, rebreathing of oxygen was instituted, soda-lime being used to absorb carbon dioxide. When we first employed the method five years ago a mouthpiece of glass or rubber was inserted between the lips and teeth. The patient breathed oxygen through his mouth and diluted this with air from his nose. It was more comfortable than a mask but many patients objected to its use over long periods. Furthermore, regulation of the oxygen concentration was difficult. Recently, we have substituted glass nose-pieces of varying size which are connected in circuit as the mouthpiece was. It consists of two glass tubes which fit into each nostril at one end and fuse at the other to make a single large glass tube, which is connected by appropriate tubing to the rest of the apparatus. For the average case one of the glass tubes is closed by a small cork and is not

used, and the other fits accurately into one nostril. In this way the patient breathes room air through one nostril and oxygen through the other.

Often a piece of thin rubber tubing about 5 inches (12.7 cm) in length and of the same diameter as the glass tubing is led off from the nose-piece and inserted into the nostril. This allows more movement on the part of the patient without disturbing the breathing of oxygen.

Theoretically, this affords a final mixture in the nasopharynx of 60 per cent oxygen, but actual measurements by catheter in situ demonstrate that 40 per cent is the rule. This is due to the fact that the apparatus when treatment is begun contains room air which tends to be gradually replaced by pure oxygen from the tank, although never completely because the exhaled air contains a varying proportion of nitrogen which dilutes the oxygen coming from the tank. It is more saving of oxygen to use a large nose-piece, with only one tube inserted into a nostril than two tubes of a small nose-piece inserted into both nostrils. This method is more satisfactory both from the standpoint of providing a 40 per cent oxygen mixture and from the standpoint of comfort of the patient than any portable apparatus we have encountered. In addition 1 liter of oxygen per minute keeps the rebreathing bag full and allows for all the waste. For this reason its efficiency on the basis of cost is proportionately great, when we consider that 1 liter from the nasal catheter provides a 25 per cent oxygen mixture. When patients breathe wholly through their mouth the mouthpiece has to be resorted to. There are patients, however, who will not submit to any appliance to the face whatever. For them an oxygen rich atmosphere must be provided.

5 Portable Oxygen Tent—Binger and myself have recently constructed a portable oxygen tent that has many of the advantages of an oxygen chamber with the additional benefits of portability and decreased cost. It encloses the entire patient in bed, is equipped with four windows, and is ventilated by a closed circuit power box which accomplishes the removal of carbon dioxide, moisture and heat. The oxygen tent secures comfort for the patient and provides for the precise regulation of the oxygen concentration desired. Most of the results in this paper are derived from the oxygen tent and the rebreathing apparatus.

RESULTS

Sixteen patients ill with pneumonia were treated with oxygen, ten in the portable oxygen tent and six by a combination of rebreathing apparatus and nasal catheter. These patients were selected because of the presence of arterial anoxemia. A summary of the clinical and laboratory data is given in Table 5. The individual case histories follow.

TABLE 5—Effect of Oxygen Treatment on Arterial Blood Gases and Clinical Conditions in Sixteen Cases of Pneumonia

Case	Age	Diagnosis	Date	Oxygen Administration	Arterial Oxygen Content, % by Volume	Oxygen Capacity, % by Volume	Arterial Oxygen Saturation, %	Arterial Carbon Dioxide Content, % by Volume	Cyanosis	Pulse Rate	Respiration Rate	Temperature	Remarks
1	48 yr	Lobar pneumonia, chronic alcoholism, drug addict, bilateral inguinal hernia	1/29/25	None	10.6	14.5	73.1	41.2	+++	128	60	103.0	Marked dyspnea, shallow breathing, pain in chest
			1/30/25	Nasal catheter, 24 hours	9.4	13.9	67.6	42.5	+++	126	62	104.0	Marked dyspnea, shallow breathing, prostration, delirium
			1/31/25	Chamber, 40% oxygen	11.9	13.9	85.5	46.5	+	120	50	103.0	After first four hours in chamber, pulse dropped to 112, respiration 48
			2/ 2/25	Chamber, 50% oxygen	—	—	—	—	0	105	44	100.0	Dyspnea much better, delirium tremens, taken out of chamber
			2/24/25	None	15.1	15.4	98.0	46.2	0	78	20	98.6	Convalescent, recovered
			12/22/24	Nasal catheter, 24 hours	14.7	17.9	82.0	29.0	++	100	40	102.0	Marked dyspnea, very feeble and weak, put in oxygen chamber
2	60 yr	Lobar pneumonia, general arteriosclerosis	12/23/24	Chamber, 40% oxygen	14.8	16.4	90.3	30.0	0	80	32	98.6	Dyspnea much better, still very weak
			12/24/24	Chamber, 40% oxygen	—	—	—	—	0	92	38	100.0	Marked weakness, dyspnea increasing
			12/24/25	None for 3 hr	11.0	15.0	73.4	29.0	+++	120	58	103.0	Dyspnea and weakness excessive, appeared hopelessly ill with new consolidation
			12/26/24	Chamber, 40% oxygen	13.5	15.0	90.0	31.0	0	110	48	102.5	Dyspnea better, still very weak
			12/29/24	Chamber, 40% oxygen	—	—	—	—	0	82	28	99.2	Gradual improvement last three days, taken out of chamber
			1/ 9/25	None	12.8	13.1	97.6	42.3	0	80	22	98.6	Convalescent, recovered
3	38 yr	Lobar pneumonia, acute appendicitis, appendectomy	3/ 5/25	None for 2 hr	12.1	16.4	73.8	47.2	++	130	50	103.0	Marked dyspnea and restlessness, nose piece used for two previous days
			3/ 5/25	Nasal catheter, 1 hour	11.7	17.1	68.5	46.8	+++	140	54	103.0	Dyspnea excessive, gurgling breathing, profuse perspiration
			3/ 6/25	Chamber, 50% oxygen	15.5	17.2	90.2	51.5	0	88	32	100.4	Dyspnea much better, marked general improvement
			3/ 7/25	Chamber, 50% oxygen	—	—	—	—	0	80	30	100.0	Comfortable but weak, taken out of chamber, recovered
4	51 yr	Lobar pneumonia, pulmonary edema	11/30/24	None	14.3	30.3	70.4	37.0	+++	140	30	103.8	Gurgling respiration, very toxic
			12/ 1/24	Nasal catheter, 5 hours	15.5	19.8	78.2	37.0	+++	145	36	102.4	Gurgling respiration, comatose
			12/ 1/24	Chamber, 48% oxygen	—	—	—	—	++	145	38	102.4	Died four hours later, circulatory failure

TABLE 5—Effect of Oxygen Treatment on Arterial Blood Gases and Clinical Condition in Sixteen Cases of Pneumonia—Continued

Case	Age	Diagnosis	Date	Oxygen Administration	Arterial Oxygen Content, % by Volume	Oxygen Capacity, % by Volume	Arterial Oxygen Saturation, %	Arterial Carbon Dioxide Content, % by Volume	Cyanosis	Pulse Rate	Respiration Rate	Temperature	Remarks
5	5	Acute tuberculous pneumonia chronic pulmonary tuberculosis	12/ 6/24	None	14.5	16.0	90.6	39.0	+	106	38	104.2	Moderate dyspnea, face pale
			12/ 7/24	Nasal catheter, 18 hours	14.1	16.0	88.2	37.0	+	106	38	104.4	Unchanged, put in oxygen chamber
			12/ 8/24	Chamber, 40% oxygen	15.0	16.0	93.8	42.5	0	94	34	104.0	Face and ears pink, moderate dyspnea
			12/ 9/24	None for 4 hr	12.7	15.7	81.0	43.4	++	98	36	103.0	Face pale, dyspnea increased
			12/10/24	Chamber, 40% oxygen	—	—	—	—	0	92	34	103.0	Face pink, tuberculosis bacillus found in sputum
6	16 mo	Lobar pneumonia, group	12/12/24	None	11.7	14.6	80.2	40.0	++	96	32	104.0	Face pale, moderate dyspnea
			12/12/24	Nasal catheter	—	—	—	—	++	96	32	104.0	Unchanged
			1/18/25	None	8.8	9.8	89.8	54.6	+	110	24	102.0	Tuberculosis in right upper and right lower lobes, recovered as chronic tuberculosis
			2/ 9/25	Nasal catheter	—	—	—	—	+++	168	76	103.6	Dyspnea intense, face dusky
			2/ 9/25	Chamber, oxygen, 40%	—	—	—	—	+	144	56	104.0	After oxygen for three hours, pulse readily palpable
7	7 yr	Lobar pneumonia	2/10/25	Chamber, oxygen, 40%	—	—	—	—	+	134	50	103.6	Dyspnea less marked, restlessness diminished
			2/15/25	Chamber, oxygen, 40%	—	—	—	—	0	104	32	100.0	Dyspnea slight, removed from chamber, recovered
			2/10/24	None	—	—	—	—	+++	145	50	104.0	Face had a grayish pallor, marked dyspnea
			2/10/24	Chamber, oxygen, 40%	—	—	—	—	0	120	38	103.6	After oxygen for four hours, dyspnea obviously diminished
			2/11/24	Chamber, oxygen, 40%	—	—	—	—	0	90	24	99.0	Crisis during night, removed from chamber, recovered
8	27 yr	Lobar pneumonia, typhoid fever	11/24/24	None	—	—	—	—	+++	120	40	102.5	Marked prostration, dyspnea and weakness
			11/25/24	Nasal catheter, 16 hours	14.0	16.7	83.8	45.0	+++	118	38	102.8	Unchanged except for slight improvement in color
			11/26/24	Rebreathing apparatus	14.8	15.4	96.1	45.0	0	110	30	102.4	Dyspnea and color much better
			11/28/24	Rebreathing apparatus	—	—	—	—	0	106	30	103.0	Oxygen stopped, recovery from pneumonia and typhoid

9	70 yr	Lobar pneumonia, pulmonary edema, general arteriosclerosis, senility	1/19/25 1/20/25 1/20/25	None Nasal catheter, 12 hours Rebreathing apparatus, 3 hr	13 0 12 1 13 8	15 7 16 5 16 4	82 8 73 5 84 2	38 0 42 0 43 0	++ +++ ++	116 120 124	35 45 30	103 5 102 8 102 0	Moderately dyspneic, feeble Increased dyspnea, gurgling respiration Gurgling respiration continued, died
10	35 yr	Lobar pneumonia	2/ 9/25 2/10/25 2/11/25 2/16/25	None Nasal catheter, 24 hours Rebreathing apparatus Rebreathing apparatus	13 0 14 2 15 7 18 0	15 4 17 1 17 5 18 3	84 5 83 0 89 8 98 4	40 4 43 6 44 0 46 7	++ ++ + 0	120 120 120 112	35 35 30 35	104 4 104 5 104 2 104 0	Dyspnea slight, apathetic, jaundiced Unchanged More toxic in appearance Irrational, otherwise unchanged, died
11	24 yr	Lobar pneumonia, empyema	2/21/25 2/21/25 2/22/25 3/16/25	None Nasal catheter, 5 hours Rebreathing apparatus None	12 9 13 8 12 7 14 0	15 7 15 7 14 1 14 5	82 2 87 9 90 1 96 5	49 5 52 0 52 0 46 1	++ + 0 0	112 100 100 90	40 38 34 20	103 5 103 8 103 5 98 6	Dyspnea slight, moderate prostration Unchanged Unchanged Recovered after empyema operation
12	62 yr	Lobar pneumonia	12/29/24 12/29/24 1/25/25	None Nasal catheter None	11 4 12 0 13 8	14 0 14 0 11 2	81 5 85 7 97 2	37 0 37 0 46 5	+++ ++ 0	112 112 82	40 40 22	103 0 103 0 98 6	Dyspnea moderate Unchanged dyspnea, color better Convalescent, recovered
13	17 yr	Lobar pneumonia	3/13/25 3/14/25	None Nasal catheter	14 4 13 3	16 8 14 8	85 8 89 9	44 1 46 6	+ 0	130 110	35 35	104 5 104 0	Moderate dyspnea, serum treated Dyspnea a little less, recovered
14	17 yr	Lobar pneumonia	3/18/25 3/19/25 3/22/25	Nasal catheter Chamber, oxygen, 50% Chamber, oxygen, 50%	12 5 17 0 —	19 8 19 0 —	63 2 89 5 —	55 8 53 3 —	+++ + 0	120 110 100	28 24 24	102 4 102 0 100 0	Delirious, very restless and toxic, nails very blue Quiet, no dyspnea Removed from chamber, recovered
15	62 yr	Lobar pneumonia, arteriosclerosis, hypertension	3/29/25 3/30/25	None Chamber, oxygen, 50%	12 2 15 4	16 8 16 9	72 6 91 2	42 5 49 0	+++ 0	110 100	32 20	101 6 99 6	Marked prostration, nails very blue Marked prostration, nails pale, died
16	40 yr	Lobar pneumonia	4/ 1/25 4/ 2/25	None Chamber, oxygen, 50%	13 8 15 4	16 8 16 9	82 1 91 2	47 4 49 5	+++ 0	130 130	36 32	103 0 103 0	Marked prostration Marked prostration and weakness, died

REPORT OF CASES

CASE 1—A colored man, aged 48, became sick four days before admission with chills and fever, pain in the side, bloody expectoration and difficult breathing. The previous history disclosed that he was a chronic alcoholic and morphin addict. Physical examination showed a man of middle age sitting propped up in bed, with great dyspnea, the rate being 60 and the breathing very shallow. Lung signs indicated consolidation of the right middle lobe and the right lower lobe. The abdomen was distended, the liver palpably enlarged, and there was bilateral inguinal hernia. The white blood cells totaled 19,700, polymorphonuclears, 85 per cent. A sputum culture yielded pneumococcus Type II. A blood culture was sterile.

The arterial oxygen saturation on admission was 73.1 per cent. Oxygen was administered for twenty-four hours by nasal catheter at approximately 1 liter per minute. The dyspnea, however, appeared even worse, and the patient became delirious. The oxygen saturation of the arterial blood with the catheter in situ was 67.6 per cent. He was put in the chamber on the fifth day of the disease, with the oxygen concentration kept at 40 per cent. In four hours his pulse had dropped from 128 to 112 and the respiratory rate from 62 to 48. The dyspnea was obviously diminished. On the following day his arterial oxygen saturation was 85.5 per cent in the chamber. He remained in the chamber in all five days, when his convalescence seemed assured. Recovery followed, complicated by delirium tremens.

In this patient a grave prognosis appeared justified by the history of chronic alcoholism and morphinism, the marked prostration and delirium, and the excessive dyspnea of the rapid, shallow type. Oxygen by nasal catheter did not affect the clinical condition or the oxygen content of the arterial blood. As a result of breathing 40 per cent oxygen, a drop in pulse and respiration rate occurred independent of any fall in temperature, with an increase in arterial oxygen saturation. It is to be noted that the arterial oxygen saturation was not brought to the normal level although it was substantially elevated. Perhaps in this case a concentration of 60 per cent in the chamber might have produced even better results.

CASE 2—A man, aged 60, following a cold became ill with cough, fever and difficulty in breathing. The course became progressively worse for five days, then the patient entered the hospital. Physical examination showed an old feeble negro sitting propped up in bed, breathing rapidly and with obvious distress. The lung signs indicated consolidation of the right lower lobe and the left lower lobe. The abdomen was distended, and the liver palpably enlarged. The white blood cells totaled 16,500, polymorphonuclears, 92 per cent, red blood cells, 3,690,000, and hemoglobin, 70 per cent. The urine had a faint trace of albumin with granular casts. A sputum culture yielded pneumococcus Type IV. A blood culture was sterile.

During the next five days the patient's dyspnea and weakness increased. Oxygen was administered by nasal catheter, approximately 1 liter per minute. Arterial oxygen saturation on the tenth day of illness was 82 per cent with the catheter in situ. The patient was then placed in the chamber, and the oxygen concentration kept at 40 per cent. In three hours the pulse dropped from 100 to 88, without a fall in temperature or respiratory rate. On the following day the patient seemed better. The arterial oxygen saturation was 90.3 per cent. The temperature remained down for one day and again rose with the recurrence of severe prostration, dyspnea and weakness. On the fifteenth day of the

disease, the pulse which had previously been good, became thready and intermittent and the rate 120. Three unsuccessful exploratory chest punctures were made to look for a possible empyema, suggested by the clinical course and the roentgenograms. The patient seemed hopelessly ill, respirations having mounted to 58. The arterial oxygen saturation out of the chamber was 73 per cent. That night the oxygen concentration of the chamber was raised to 45 per cent. On the following day, with persistent temperature, there was considerable improvement in the general appearance, as well as a fall in pulse and respiratory rate, arterial oxygen saturation was 90 per cent. Two days later the patient had improved markedly and was removed from the chamber with a normal temperature, a pulse rate of 86 and respiratory rate of 28.

This patient seemed desperately ill when oxygen treatment was begun. His prostration and weakness throughout the entire course of illness was marked. It appeared that the seven days that he spent in the chamber tided him over until he developed sufficient antibody. When out of the chamber on the fifteenth day for exploratory chest punctures and for roentgen-ray examination of the chest, his dyspnea was at its worst. Several hours later, breathing 45 per cent oxygen, there was noticeable improvement in the breathing and later in the night in the pulse. Oxygen by nasal catheter did not seem to be of much help, the arterial oxygen saturation being 82 per cent with the catheter in situ, and on two occasions being 90 per cent in the chamber. It is of considerable interest that the arterial carbon dioxide content rose from 29 per cent by volume to 42.3 per cent by volume during convalescence, this suggests a lowered alkaline reserve during the acute stage of the illness.

CASE 3—A man, aged 38, two and a half weeks after an operation for removal of the appendix, developed a cough, rusty sputum and a temperature of 104. Physical examination showed a thin, adult man, in moderate dyspnea and slightly cyanotic. The lung signs indicated consolidation of the right lower lobe. White blood cells totaled 15,800, polymorphonuclears, 90 per cent. The sputum contained no pneumococci. A blood culture was sterile. On the fifth day of the disease dyspnea, cyanosis and prostration had increased and oxygen was given with the rebreathing apparatus, using the nose-piece. A second sputum examination revealed pneumococcus Type I, and a blood culture was positive for pneumococcus Type I. Serum treatment was begun. On the sixth day consolidation spread to the left lower lobe, the right middle lobe and the right upper lobe, with no signs of resolution in the right lower lobe. The patient grew rapidly worse. He objected to the nose-piece and oxygen by this method was discontinued. One hour later the arterial oxygen saturation was 73.8 per cent, and gurgling respiration had developed. The use of a nasal catheter for one hour at 2 liters per minute resulted in no perceptible change, the arterial oxygen saturation with the catheter in situ being 68.5 per cent. The patient was then put in an oxygen tent, the concentration of oxygen being kept at 50 per cent. Four hours later decided improvement was manifest. His rebreathing was easier, the nails were somewhat pink, the pulse had slowed, and there was no gurgling in the throat. Serum treatment was resumed and on the following day the temperature began to fall. The arterial oxygen saturation was 90.2 per cent. The patient was kept in the tent in all three days, when he was removed convalescent. Subsequently, he was operated on for empyema.

On the sixth day of disease this patient had a positive blood culture, with the left upper lobe uninvolved by consolidation. The arterial oxygen saturation at its lowest was 68.5 per cent. He would tolerate no use of any portable oxygen apparatus. The nasal catheter did not raise the oxygen content of the arterial blood. The inhalation of 50 per cent oxygen in the tent increased his arterial oxygen saturation to 90.2 per cent and was followed by unmistakable clinical improvement. During his residence in the oxygen tent, massive serum treatment was followed by a sterile blood culture and the crisis. It seemed probable that oxygen treatment tided the patient to a period when a specific immunity was established with the help of serum administration.

CASE 4—A man, aged 51, six days before admission became sick with chills, fever and cough. Physical examination showed a well developed man, intensely cyanotic and dyspneic, with loud, gurgling respiration. The lung signs indicated consolidation of the left lower and the right upper lobes. Heart sounds were inaudible. The white blood cells totaled 20,800, polymorphonuclears, 93 per cent. A sputum culture yielded pneumococcus Type III, and a blood culture was positive for pneumococcus Type III. Oxygen was administered through a nasal catheter at about 15 liters per minute, with slight lessening of cyanosis and increase of arterial oxygen saturation from 70.4 to 78.2 per cent. The pulse became thready and intermittent. After four hours of catheter oxygen treatment, he was put in the oxygen chamber, which was kept at 45 per cent oxygen. For a short while cyanosis perceptibly diminished, but subsequently became worse as the pulse became impalpable, the cyanosis then being largely due to a venous anoxemia. The patient died four hours later of circulatory failure.

In this patient, a man of 51 years, edema of the lungs occurred on the sixth day of the disease with the presence of pneumococcus Type III in the blood stream. Circulatory failure was imminent when he was put in the tent. He made no response to oxygen treatment.

CASE 5—A man, aged 19, following a cold had a severe chill and soon after cough, pain in the side and blood streaked sputum. The symptoms persisted for ten days, when he entered the hospital. Physical examination showed a young, well developed man with moderate dyspnea and slight cyanosis of the nail beds. The lung signs indicated consolidation of the right lower lobe, the right middle and the right upper lobes. The white blood cells totaled 11,100, polymorphonuclears, 84 per cent. A sputum examination revealed pneumococcus Type IV, a blood culture was sterile.

On the third day after admission, the arterial oxygen saturation was 92.5 per cent. Oxygen was administered by a nasal catheter at approximately 1 liter per minute for twenty-four hours, at which time the arterial oxygen was 88.2 per cent. On the next day in the tent, the oxygen concentration was at 40 per cent, the arterial oxygen was 93.8 per cent. On the following day, the sixth day after admission, the patient was taken out of the chamber for four hours, at the end of which time considerable cyanosis had developed and the arterial oxygen had fallen to 81 per cent. On the seventh day in the tent cyanosis cleared, and on the eighth day out of the tent cyanosis returned. A nasal catheter at 1 liter per minute did not change the cyanosis. On the sixth day of disease, tubercle bacilli were found in the sputum. The patient was subsequently transferred to the roof, where treatment of chronic pulmonary tuberculosis of the right upper and the right lower lobes was carried on.

In this patient anoxemia was constantly cleared by inhalation of 40 per cent oxygen in the tent, whereas the nasal catheter was without effect. This patient turned out to have pulmonary tuberculosis, at the onset apparently an acute tuberculous pneumonia. His respiratory embarrassment was only moderate through his illness.

CASE 6—A girl, aged 16 months, was sick four days before admission with fever and rapid, grunting respiration. Physical examination showed a cyanotic infant breathing with great distress. The pulse was 145, respiration, 55, and temperature, 105. The lung signs indicated consolidation of the right upper lobe. The white blood cells totaled 9,500, polymorphonuclears, 70 per cent, and hemoglobin, 55 per cent. The sputum contained a streptococcus. The patient seemed to grow steadily worse and on the ninth day consolidation spread to the right middle lobe. The pulse became thready and intermittent, the rate being 168, respiration was very shallow, the rate, 74. The nail beds were deeply cyanotic, the face had a dusky grayish pallor. Oxygen by nasal catheter was attempted, but the child tossed from side to side and continually pulled it out. She was put in the oxygen chamber, the oxygen concentration being kept at 40 per cent. In three hours the pulse was fuller and stronger, the rate 144. Respiration seemed easier, the rate 56. Cyanosis was very much diminished. The patient was kept in the chamber six days when convalescence seemed assured.

This patient gave every evidence of being moribund on the ninth day of illness. The inhalation of 40 per cent oxygen was followed by obvious improvement in subjective well-being, manifested by quietness instead of extreme restlessness, by slowing of both pulse and respiration and by the clearing of the cyanosis. She had to be kept in the tent six days before the dyspnea seemed sufficiently relieved so that she could be without oxygen. The presence of a moderately severe anemia aggravated the arterial anoxemia. The respiratory rate, 74 before oxygen treatment, was accompanied by shallow breathing, which also probably enhanced the oxygen deficiency. This was the highest respiratory rate that we have encountered.

CASE 7—A girl, aged 7 years, following a cold in the head of one week's duration, had a chill and shortly after a severe pain in the left side. The next day she entered the hospital with a temperature of 105, pulse, 150, and respiration, 32. The lungs showed consolidation of the right lower lobe. She developed profuse bleeding from the nose. On the sixth day she appeared very prostrated. Consolidation had spread to the left lower lobe. The face was very pale with slight cyanosis of the lips and moderate cyanosis of the nail beds. The temperature was 104, the pulse, 145, and respiration varied between 44 and 45. She was put in the oxygen chamber, the oxygen concentration at 40 per cent. The cyanosis cleared and the respirations lost their grunting quality, the rate varying between 36 and 40. At the end of twenty-four hours, the crisis occurred with the subsidence of constitutional symptoms, and the patient was removed from the chamber.

In this patient a critical period of acute respiratory embarrassment on the sixth day of disease was relieved by the inhalation of 40 per cent oxygen. The disappearance of restlessness and of the grunting quality to expiration occurred three hours after she was put in the tent.

CASE 8—A woman, aged 27, became ill eight days before admission with malaise, headache and fever. There was no history of cough, chill or pain in the chest. Physical examination showed a thin young woman, prostrated and breathing in a rapid, shallow manner without expiratory grunt. There was slight cyanosis of the nail beds. The lung signs indicated consolidation of the right lower and the left lower lobes. The abdomen disclosed numerous rose spots. The white blood cells totaled 5,100, polymorphonuclears, 56 per cent. A blood culture grew *Bacillus typhosus*. No sputum was obtainable.

On the tenth day of disease cyanosis became deep, with extreme dyspnea and prostration. A nasal catheter for sixteen hours produced barely perceptible lessening of cyanosis. On the eleventh day oxygen was begun with the nose-piece rebreathing apparatus, the patient obtaining approximately a 60 per cent oxygen mixture, at first continuously and later thirty minutes of each hour. Improvement was striking in four hours. She felt relieved of dyspnea, the color improved, and the general appearance of prostration visibly diminished. The arterial oxygen saturation was increased from 83.8 per cent, during catheter administration, to 96.1 per cent during nose-piece administration. Oxygen was given through the nose-piece at intervals for three days, when acute respiratory distress was alleviated. The patient subsequently recovered from typhoid.

The masking of the symptoms of pneumonia by typhoid fever was typically observed in this patient. There was no cough, sputum, pain in the chest, expiratory grunt, or onset with chill. The period of acute respiratory distress appeared to be tided over by administration of 60 per cent oxygen, with the nose-piece apparatus, after the nasal catheter had failed to alleviate substantially the cyanosis, the dyspnea or the arterial anoxemia. Massive consolidation was present in both lower lobes, but owing to the entire absence of sputum the organism could not be determined.

CASE 9—A woman, aged 70, following a fall developed a pain in the left chest and a cough productive of rusty sputum. She entered the hospital on the fourth day of the disease. Physical examination showed a woman in advanced senility, moderately dyspneic and cyanotic. The lungs showed consolidation of the right lower lobe. The heart was slightly enlarged, with a systolic murmur at the apex. The white blood cells totaled 21,700, polymorphonuclears, 91 per cent. A blood culture was sterile. Sputum was not obtained. Oxygen was administered through a nasal catheter at approximately 1 liter per minute. The patient grew steadily worse with the development of moisture in her throat. The arterial oxygen saturation fell from 82.8 per cent before the use of the catheter to 73.5 per cent with the catheter in situ. When the nose-piece was applied with the rebreathing apparatus, the arterial oxygen saturation rose to 84.2 per cent in three hours, without other signs of improvement. She died twenty-four hours later of circulatory failure.

In this patient, a woman in advanced senility, lobar pneumonia set in after a severe fall. Catheter oxygen treatment failed to arrest the progressive arterial anoxemia. The nose-piece rebreathing apparatus, providing approximately a 40 per cent oxygen mixture, raised the arterial oxygen saturation from 73.5 to 84.2 per cent, still far from the normal level. However, no improvement in the clinical condition was apparent from the oxygen treatment.

CASE 10—A man, aged 55, following a head cold was suddenly seized with a chill, pain in the right side and cough four days prior to admission. Physical examination showed a well developed man acutely ill, in considerable prostration, jaundiced, slightly cyanotic, and moderately dyspneic. The lung signs indicated consolidation of the right upper, the right lower and the right middle lobes. A sputum examination showed pneumococcus Type IV. A blood culture was sterile. The white blood cells totaled 13,000, polymorphonuclears, 82 per cent. Oxygen was administered by nasal catheter at 1 liter per minute for twenty-four hours, the arterial oxygen saturation changing from 84.5 to 83 per cent. With the nose-piece rebreathing apparatus, the arterial oxygen saturation was raised to 89.8 per cent. Oxygen was administered for eight days by the nose-piece rebreathing apparatus for from twenty to thirty minutes of each hour. At the end of eight days the temperature gradually fell to normal. When convalescence seemed assured the patient developed a recurrent infection and died a month later of a pneumococcus Type IV bacteremia. The focus was not determined.

In this patient oxygen lack was at no time severe. The nasal catheter failed to elevate the arterial oxygen saturation and the rebreathing apparatus, providing about 40 per cent oxygen, increased it only moderately. No effect was observed in the clinical condition as a result of oxygen treatment.

CASE 11—A woman, aged 24, was suddenly seized with a chill, followed by pain in the left side of the chest and cough. On the sixth day of illness, she also developed a pain in the right side of the chest, and entered the hospital. Physical examination showed a poorly nourished young woman, moderately dyspneic and slightly cyanotic. The lung signs indicated consolidation of the right lower and the left lower lobes. The white blood cells totaled 19,200, polymorphonuclears, 91 per cent. The sputum contained a hemolytic streptococcus.

The arterial oxygen saturation was 82.2 per cent. Oxygen was administered by a nasal catheter for five hours at 2 liters per minute, at which time arterial oxygen saturation was raised to 87.9 per cent. From this time on the rebreathing apparatus was used, the patient breathing through the nose-piece. On the following day the arterial oxygen saturation was 90.1 per cent during administration through the nose-piece. Thoracotomy was subsequently performed for empyema of the left pleural cavity. The patient made a good recovery.

The nasal catheter administration at 2 liters of oxygen per minute elevated the arterial oxygen saturation from 82.2 to 87.9 per cent. After inhalation of 50 per cent oxygen through a nose-piece rebreathing apparatus, the arterial oxygen saturation was 90.1 per cent. Since the catheter here furnished approximately 30 per cent oxygen in the inspired air, it is seen that a measurable improvement may result from this concentration. The patient did not appear severely ill at any time.

CASE 12—A man, aged 62, two days before admission developed pain in the chest, fever and cough. Physical examination showed a well developed man, moderately dyspneic and cyanotic. The lung signs indicated consolidation of the right upper and the right middle lobes. The white blood cells totaled 17,200, polymorphonuclears, 86 per cent. Sputum examination showed pneumococcus Type IV. A blood culture was sterile.

Oxygen through a nasal catheter was administered on the sixth day of illness, with slight improvement in the color and increase of the arterial

saturation from 81.5 to 85.7 per cent. Catheter oxygen treatment was continued until convalescence.

In this patient administration of oxygen by catheter at a rate of 2 liters of oxygen a minute, furnishing approximately 30 per cent oxygen in the inspired air, caused a slight increase in arterial oxygen saturation, from 81.5 to 85.7 per cent, still 10 per cent below the normal value.

CASE 13—A boy, aged 17 years, seventeen hours before admission was seized with a shaking chill, pain in the left side of the chest and had bloody sputum. Physical examination showed a well developed boy, somewhat dyspneic and slightly cyanotic. The lungs sign indicated consolidation of the left lower lobes. The white blood cells totaled 24,200, polymorphonuclears, 90 per cent. Sputum examination showed pneumococcus Type I. On the third day serum treatment was begun. Oxygen was administered by nasal catheter at 2 liters per minute, increasing the arterial oxygen saturation from 85.8 to 89.9 per cent.

Catheter oxygen treatment resulted in a moderate elevation of the arterial oxygen saturation. In this instance at 2 liters per minute the inspired air contained 30 per cent oxygen. There was an uneventful recovery.

CASE 14—A boy, aged 14 years, was suddenly seized with a severe chill, followed by a sharp pain in the left side. On the following day cough began, with blood streaked sputum, and the patient entered the hospital. Physical examination showed a prostrated boy with little dyspnea and slight cyanosis. The lung signs indicated consolidation of the left lower lobe. The white blood cells totaled 15,300, polymorphonuclears, 96 per cent. Sputum examination showed pneumococcus Type I. A blood culture was sterile. Serum treatment was instituted. On the fifth day consolidation extended to the right lower lobe and the patient became irrational, very toxic and cyanotic, use of a nasal catheter was attempted at 2 liters of oxygen per minute, but the patient would not tolerate it.

The arterial oxygen saturation with the nasal catheter in situ was 63.2 per cent. He was placed in an oxygen tent, the oxygen concentration being kept at 50 per cent. The cyanosis cleared, the respirations fell from 28 to 14, the pulse from 120 to 110, and the patient lost active delirium. On the following day the arterial oxygen saturation was 89.5 per cent. The patient was in the chamber four days, when convalescence was established.

In this patient an extension of consolidation on the fifth day of the disease was attended with active delirium, deep cyanosis and marked prostration. Catheter oxygen treatment was unsuccessful both in raising the oxygen content of the arterial blood and in alleviating the clinical signs of respiratory embarrassment. The inhalation of 50 per cent oxygen in the tent was followed by an elevation of the arterial oxygen from 63.2 to 89.5 per cent, a clearing of cyanosis, a fall in the respiratory rate from 28 to 14, a decrease in the pulse rate from 120 to 110, and a striking diminution in delirium and restlessness. Convalescence occurred after four days in the tent.

CASE 15—A woman, aged 62, felt poorly for three days, when she developed a frequent cough, with blood streaked sputum and fever. She entered the hospital on the following day. Physical examination showed an old woman, who appeared at least 70, in slight dyspnea, without cyanosis or prostration. The lungs showed beginning consolidation of the right lower lobe. The heart was enlarged to the left, with numerous premature contractions. The systolic blood pressure was 185, the diastolic 80. The patient had general arteriosclerosis. The white blood cells totaled 21,800, polymorphonuclears, 84 per cent. Sputum examination showed pneumococcus Type III. During the next five days consolidation spread to the right upper, the right lower and the right middle lobes, and edema of the lungs began. A blood culture was positive for pneumococcus Type III.

The arterial oxygen saturation was 72.6 per cent. She was put in the oxygen tent, the oxygen concentration being kept at 50 per cent. On the following day the arterial oxygen was 91.2 per cent. The respiratory rate had decreased from 36 to 20, and the pulse from 110 to 100. Edema of the lungs persisted, and the patient seemed to grow steadily weaker. On the following morning she was taken out of the tent for a short time and deep cyanosis returned, with immediate acceleration of the respiratory rate to 36. When she was replaced in 50 per cent oxygen, the color returned and the respiratory rate slowed. The pulse rate had gradually risen during the night to 160 and at noon became impalpable, and the patient died.

This patient was in the hospital from the first day of disease. Although she gave her age as 62 she seemed at least ten years older. The invasive power of pneumococcus Type III in this instance could be watched from day to day, as consolidation involved progressively every lobe except one, with the organism present in the blood stream. The inhalation of 50 per cent oxygen slowed her respiratory rate to 20 and brought the arterial oxygen almost to the normal level. The pulse on the first day in the tent was 100 and of good quality. The toxic appearance, however, never left her, and death occurred as a result of cardiac failure.

CASE 16—A woman, aged 40, following a cold became acutely ill with pains in the chest, cough and fever. She entered the hospital on the third day of illness. Physical examination showed a well nourished woman, considerably prostrated, moderately dyspneic and cyanotic. The lung signs indicated consolidation of the right lower lobe. The white blood cells totaled 12,200, polymorphonuclears, 92 per cent. Sputum examination showed pneumococcus Type III. A blood culture was sterile. Two days later consolidation had spread to the right middle and the left lower lobes. Dyspnea, cyanosis and prostration were worse. The arterial oxygen saturation was 82.1 per cent.

The patient was put in an oxygen tent, the oxygen concentration being maintained at 50 per cent. The cyanosis cleared and the arterial oxygen on the following day was 91.1 per cent. The patient still appeared very toxic. The pulse remained at 130, the respiratory rate changed from 36 to 32, and edema of the lungs began. A blood culture was now positive for pneumococcus Type III. The next day the pulse rose to 156, became irregular, and the patient died.

In this patient also, pneumococcus Type III was associated with progressive advancement of consolidation and blood stream infection. Prostration was marked throughout. Although arterial oxygen was elevated no clinical benefit resulted.

COMMENT

Methods—The tube and funnel may be dismissed as a relatively ineffective method. At the maximum rate at which oxygen may be practically administered, i. e., 2 liters a minute, the air in the nasopharynx contained 22 per cent oxygen, corresponding approximately to 24 per cent in the inspired air.

The nasal catheter when conscientiously employed at the rate of 1 liter per minute yielded an oxygen concentration of 25 per cent in the nasopharyngeal air. Under certain conditions, in which 2 liters of oxygen are administered, the oxygen concentration of the nasopharyngeal air may be from 30 to 33 per cent. This involves the use of a relatively large amount of oxygen and is most practicable with high pressure oxygen.

The clinical results of catheter oxygen treatment are variable. In the mild cases a measurable increase in the arterial oxygen saturation may occur, occasionally also in the severe ones, but in none is the increase up to normal level. In patients gravely ill an arterial anoxemia frequently grew worse even during the administration of oxygen by catheter, whereas the same patients were improved by the inhalation of from 40 to 60 per cent oxygen in the tent or by the rebreathing apparatus. A summary of the cases indicates that in four the arterial oxygen saturation was increased during catheter administration, in six it was stationary or decreased, and in eight an arterial oxygen saturation obtained during catheter treatment was increased above that value by the inhalation of 40-60 per cent oxygen. Although the series is small it defines the limitation of the nasal catheter, or more precisely, it defines the effectiveness of the inhalation of from 25 to 30 per cent oxygen.

These results do not indicate the maximum efficiency of catheter oxygen treatment as in some instances 1 liter of oxygen was administered instead of 2 liters in order to determine the effects of a routine use in the hospital. The catheter can usually be employed, however, under conditions that will furnish from 30 to 35 per cent oxygen in the inspired air, a concentration that is distinctly beneficial in the treatment of mild and moderate cases of anoxemia. For the relief of severe arterial anoxemia higher concentrations are generally necessary.

The rebreathing apparatus particularly with the use of the nose-piece as described appears to be an effective method of administering oxygen, providing a 40 per cent oxygen mixture without, in most cases, disturbing the patient. The employment of a single tube permits oxygen to be breathed through one nostril and air through the other. An administration of 1 liter of oxygen per minute into the rebreathing bag results in this method in a 40 per cent oxygen mixture. When mouth breathing takes place, as in many moribund cases, a mouthpiece must be used.

The portable oxygen tent has worked well in securing a precise oxygen concentration, and in not having any appliance to the face. It may be readily transported and is put up in an hour without necessarily moving the patient from his bed. We have not used it in summer, and believe it would be difficult to get adequate cooling under warm conditions of the external atmosphere.

Clinical Results—Of the ten patients treated in the tent seven recovered. The three who died all suffered from a pneumococcus Type III lobar pneumonia with pneumococcus Type III in the blood stream. Of six patients treated with the more portable apparatus, four recovered. Of the two who died one had a recurrent bacteremia a month after the acute illness. The other, a woman of 72, did not have a blood culture taken during the latter part of her illness. Thus, all of the four fatal cases that had blood cultures taken had a blood stream infection. These figures are recorded not with the idea that they have any statistical value but rather to point out the limitations of oxygen therapy. The first point brought out in this series is that the benefit of oxygen treatment may be nullified by the presence of a bacteremia.

The bacteremia due to pneumococcus Type III was associated with a progressive increase in lung consolidation and in the toxic appearance of the patient. It seemed probable that in Cases 15 and 16 oxygen treatment prolonged life but its fatal outcome appeared inevitable from the presence of a blood stream infection. In Case 3, however, a pneumococcus Type I lung involvement was associated with advancing consolidation and a blood infection of pneumococcus Type I on the sixth day of disease. The outlook in this case appeared as grave as in the foregoing cases. The improvement in the clinical condition was so marked as a result of the inhalation of oxygen as to warrant the resumption of serum treatment, which was then given in massive doses and was followed by the sterilization of the blood stream and subsequent crisis. As nearly as we can judge from sequential evidence, oxygen treatment in this instance prolonged life until the immunity factor aided by serum treatment dissipated the toxemia of the disease.

Of the ten patients treated in the tent seven recovered. Although the series is too small to have the slightest statistical value, a detailed study of six of these patients who were obviously gravely ill, reveals an unmistakable alteration in their clinical course after oxygen treatment was instituted. We may now consider some of the signs of improvement that these cases made which seemed to be related to the inhalation of from 40 to 50 per cent oxygen. The clinical and laboratory data are summarized in Table 5.

Clinically, the patient soon after his entrance into the tent appears more comfortable, with the disappearance or diminution of cyanosis, decrease of restlessness and at times relief of dyspnea. In many

instances there is a drop in the pulse or the respiratory rate or in both. Slowing of the pulse or respiration must be dissociated as far as possible from a fall in temperature in order to ascribe the effect to the inhalation of oxygen.

In Table 6 a comparison is made between the pulse and the respiratory rate before and after increase of arterial oxygen saturation. The temperature has been added for the time these observations were made (In this table some of the results of the cases not in the oxygen tent are included.)

TABLE 6—*Effect of Increasing Arterial Oxygen Saturation on Pulse and Respiration Rate*

Case	Increase of Arterial Oxygen Saturation, per Cent		Change in Pulse Rate		Change in Respiration Rate		Change in Temperature Rate	
	Before	After	Before	After	Before	After	Before	After
1	67.6	85.5	126	112	62	48	104.0	104.0
2	73.4	90.0	120	110	58	48	103.0	102.5
3	68.5	90.2	140	88	54	32	103.0	100.4
5	88.2	93.8	106	94	38	34	104.4	104.0
8	83.8	96.1	118	110	38	30	102.8	102.4
9	73.5	84.2	120	124	45	30	102.8	102.0
10	83.0	89.8	120	120	35	30	104.5	104.3
11	87.9	90.1	112	100	38	34	103.8	103.5
12	81.5	85.7	112	112	40	40	103.0	103.0
13	85.8	89.9	130	120	35	35	104.5	104.0
14	63.2	89.5	120	110	28	24	102.4	102.0
15	72.6	91.2	110	100	36	20	101.6	99.6
16	82.1	91.2	130	130	36	32	103.0	103.0

It is seen that in six cases definite slowing of the pulse and in six cases, not necessarily the same, slowing of the respiratory rate occurred unexplained by a fall in temperature. Thus, in Case 1 the pulse dropped from 126 to 112, and the respiratory rate from 62 to 48. In the foregoing case histories, instances are found in which the fall in the respiratory rate and the pulse rate took place during several hours immediately after inhalation of from 40 to 50 per cent oxygen, viz., Cases 1, 2, 3, 6 and 14, instances in which improvement of respiration and pulse was definitely related to the inhalation of an oxygen rich atmosphere. It is to be noted that in no instance did the pulse rate approach normal, a fall of from 8 to 14 beats being the usual drop in those in which slowing occurred at all. However, in the infant in this series the pulse before oxygen treatment was 168, of very poor quality and at times intermittent, and three hours later in 45 per cent oxygen was 144 and of good quality.

The slowing of the respiration when it occurs is likewise apt to be between 6 and 14 per minute, with from 8 to 10 a fair average. As a rule the slowing of the respiratory rate does not approach normal, but two cases were so reduced. Cases 14 and 15. In the first, respirations dropped from 28 to 14 and in the second from 36 to 20.

From the data obtained in this series and from earlier investigations it may be said that the slowing of the pulse is of more frequent occurrence as a result of oxygen inhalation than slowing of the respiratory rate, and occurs in more than half the cases. It may be of small degree, such as from 4 to 8 beats a minute, and may be ascertained only by careful counts before oxygen inhalation and at frequent intervals during the ensuing several hours. The four hour temperature chart may not show these differences. In severely anoxic cases, as has been pointed out, a more striking drop in pulse rate may be expected.

The slowing of the respiratory rate as a result of oxygen inhalation appears to occur approximately in half the cases, being more striking and more frequent in the severe cases. The relief of dyspnea is apt to be associated with the decreased rate rather than a decrease in tidal air.⁸ This was clearly shown in a case of Binger²⁰ in which the pulmonary ventilation was determined when the patient was in the oxygen chamber one day and exposed to room air the following day.

It may be mentioned that in all the cases studied an increase in arterial oxygen saturation was effected by the inhalation of from 40 to 60 per cent oxygen but that in only two cases was the arterial oxygen brought to the normal level. In the severe cases of arterial anoxemia, from 89 to 91 per cent saturation was the usual maximum achieved by oxygen treatment. Most of these cases represented the severest types of anoxemia seen in routine ward services and were selected for this reason. Substantial elevation of the oxygen content was nevertheless produced. These observations are in accord with earlier investigations.¹

It is of some interest to examine the determinations of the arterial carbon dioxide content in these cases. The average for normal persons Peters, Barr and Rule²¹ found to be 49.3 per cent by volume. Of the fourteen cases in this series five were above 45 per cent by volume, five between 40 and 45 per cent by volume, and five below 40 per cent by volume. In other words, in five of fourteen patients a distinct decrease in the carbon dioxide content of the arterial blood was present. In one case only was this severe, Case 2, in which the arterial carbon dioxide content was 29 per cent by volume. As convalescence was reached the carbon dioxide content manifested a distinct tendency to rise toward normal, thus, in Case 1, from 41.2 to 46.2 per cent by volume, in Case 2, from 29 per cent by volume to 42.3 per cent by volume, in

20 Binger, C. A. L., Hastings, A. B., and Neill, J. M. Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, *Arch. Int. Med.* **31**: 145 (Jan.) 1923.

21 Peters, J. P., Barr, D. P., and Rule, F. D. Carbon Dioxide Absorption Curve and Carbon Dioxide Tension of Blood of Normal Resting Individuals, *J. Biol. Chem.* **45**: 489 (Feb.) 1921.

Case 5, from 39 per cent by volume to 54.6 per cent by volume, and in Case 12 from 37 per cent by volume to 46.5 per cent by volume.

It is beyond the scope of this article to review the question of acidosis in pneumonia. A decrease in the fixed alkali of the blood as well as a lowered blood p_H has been observed by some investigators, whereas others have found only normal values. Recent experiments on animals suggest that the cause of these discordant results may lie in the presence or absence of severe anoxemia. When pigs are subjected to relatively mild anoxemia, there is a fall in the blood carbon dioxide capacity with a slight alkalosis, with severe anoxemia the reduction in blood carbon dioxide is accompanied by a decided lowering of the p_H .²² In addition there is a marked increase in the excretion of organic acids in the urine. An acidosis, as evidenced by a fall in carbon dioxide capacity and arterial blood p_H , has been described in experimental pneumonia in dogs, "due chiefly to the effects of an anoxic anoxemia."²³ The patients in this study as well as in that previously reported²⁴ were generally selected because of the presence of severe arterial anoxemia.

SUMMARY AND CONCLUSIONS

1 Experiments were conducted on the efficacy of certain methods of administering oxygen by analyzing the oxygen concentration of the nasopharyngeal air, by calculating the oxygen concentration of the inspired air, and by the arterial oxygen saturation before and after treatment.

2 The tube and funnel method at its maximum efficiency raises the air in the nasopharynx to 22 per cent, and may be considered almost useless as a therapeutic agent. With oxygen administered at 2 liters per minute, the inspired air has an oxygen concentration of approximately 24 per cent.

3 The nasal catheter may vary in its effectiveness to the extent that the nasopharyngeal air may contain between 22 and 35 per cent oxygen depending largely on the rate of administration of oxygen from the tank. At 1 liter per minute the inspired air contains approximately 25 per cent oxygen. Under special conditions, including a flow of 2 liters of oxygen per minute, the inspired air contains approximately 30 per cent oxygen. The advantages of high pressure oxygen for this purpose were pointed out.

²² Brunquist, E. H., Schneller, E. J., and Loevenhart, A. S. The Effects of Anoxemia on Nitrogen Metabolism, *J. Biol. Chem.* **62** 93 (Nov.) 1924.

²³ Leake, C. D., Vickers, J. L., and Brown, T. K. Blood Reaction in Experimental Pneumonia, *J. Exper. Med.* **39** 393 (March) 1924.

²⁴ Barach, A. L., Means, J. H., and Woodwell, M. The Hydrogen Ion Concentration and Bicarbonate Level of the Blood in Pneumonia, *J. Biol. Chem.* **50** 413 (Feb.) 1922.

When catheter oxygen treatment is carried out at its maximum efficiency there is apt to be considerable increase in the oxygen saturation of the arterial blood, particularly in the mild and moderate cases of oxygen want. For the relief of severe arterial anoxemia higher concentrations of oxygen than this method affords appear to be necessary.

4 The rebreathing apparatus with the use of a specially constructed glass nose-piece is the most efficient of the easily portable types of apparatus and in most cases causes little discomfort to the patient. The mouthpiece is used at times when mouth breathing is present. With the nose-piece rebreathing apparatus 1 liter of oxygen per minute provides a 40 per cent oxygen mixture in the inspired air. Observations on the arterial blood confirm the effectiveness of the method.

5 The portable oxygen tent as devised by Binger and myself was used in the majority of cases treated. It secured an oxygen rich atmosphere capable of regulation at the precise concentration desired. It accomplished adequate removal of carbon dioxide, moisture and heat, and was comfortable for the patient to live in. In warm weather the tent was not used because of difficulty in cooling under these conditions.

6 Of ten cases treated in the oxygen tent seven recovered. The three patients who died all had pneumococcus Type III in their sputum, with pneumococcus Type III bacteremia. Of the six patients treated with a portable apparatus four recovered. Of the two who died one developed a bacteremia late in convalescence. These results indicate that the grave prognosis of a persistent bacteremia in lobar pneumonia is unaltered by the administration of oxygen.

7 All the patients except one who were treated in the oxygen tent were gravely ill. The clinical signs of improvement that were especially apt to follow inhalation of from 40 to 60 per cent oxygen were (1) clearing of cyanosis, (2) partial relief of dyspnea, (3) diminution of restlessness and promotion of sleep, (4) slowing of the respiratory rate and the pulse rate, more constant in the severe cases, and (5) a tendency to lessened delirium.

8 The arterial oxygen saturation was increased in all the tested cases. In severe arterial anoxemia the inhalation of 40-60 per cent oxygen raised the arterial oxygen saturation substantially but not to the normal level.

9 The arterial carbon dioxide content was lowered in five of fourteen cases. This decrease was severe in only one patient.

10 The value of oxygen treatment is felt to be supportive and not curative. In severe dyspnea with cyanosis, oxygen treatment has appeared to prolong life until such a time as the immunity mechanism was able to accomplish recovery. In this series six patients seemed to be aided in this manner.

GASTRIC SECRETION IN EXPERIMENTAL BERIBERI IN THE DOG *

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Clinically, a decreased gastric acidity has been reported a number of times in severe cases of beriberi. Experimentally, both a decreased acidity as well as a diminished secretion have been observed in dogs kept on a beriberi producing diet. Myadere, however, reported that in such an experimental dog the gastric glands could still be stimulated to a normal secretion by alcohol taken by mouth.

The purpose of the studies I am reporting on was, first, to confirm the change in the volume and character of the gastric secretion in experimental beriberi, second, to confirm the changes therein during a recovery from beriberi as a result of a normal or control diet, third, to determine the change, if any, in the response of the gastric secretion to such stimulants as histamin and gastrin as compared with a food stimulus, fourth, to prove that the antineuritic water soluble B is not a gastric secretagogue, and, fifth, to prove that the addition of this antineuritic vitamin to an otherwise beriberi producing diet keeps the dog in good condition.

The experimental procedure was to prepare Pawlow pouch dogs and to study the gastric secretion in these animals before and during the production of beriberi as affected by food, histamin, gastrin and Harris yeast vitamin. The beriberi producing diet was the same as the control diet with the exception that the former was autoclaved after the addition of sodium carbonate. To neutralize the base thus formed in the autoclaving process the mixture was slightly acidified with hydrochloric acid before feeding. An amount of salt equivalent to the amount thus formed was added to the control diet.

In Tables 1 and 2 are given the results showing the effect of the diet, autoclaved in an alkaline condition, on the gastric secretion of Pawlow dogs. It required from thirty-one to thirty-three days to bring about severe symptoms of beriberi, but several weeks before this a decreased secretion or a lowered acidity in gastric juice, or both, is observed.

Table 3 shows that the same diet produced beriberi in thirty days with a much earlier loss in secretion and acidity of gastric juice. This animal was brought back to a normal condition on the control diet in forty-one days, and after continuing on this for another thirty-five days was then again placed on the diet autoclaved without the addition of sodium carbonate. Although the animal had already been in the poly-

* From the Department of Physiological Chemistry, University of Chicago

TABLE 1—*Effect of Diet Autoclaved with Alkali (20 C c of 10 Per Cent Sodium Carbonate Per 400 Gm Food) on Gastric Secretion of Dog (Experiment 2)*

Date	Volume in C c for Four Hours	Average Free Acidity, per Cent Hydro- chloric Acid	Average Total Acidity, per Cent Hydro- chloric Acid	Remarks
1/19/24	20 0	0 27	0 36	Fresh diet
1/20/24	13 4	0 13	0 28	Fresh diet
1/23/24	18 2	0 29	0 37	Fresh diet
1/26/24	15 5	0 18	0 31	Autoclaved diet first day
1/29/24	18 4	0 18	0 28	Autoclaved diet fourth day
2/ 2/24	13 0	0 06	0 16	Autoclaved diet eighth day
2/ 3/24	20 2	0 17	0 25	Autoclaved diet ninth day
2/ 4/24	13 0	0 13	0 22	Autoclaved diet tenth day
2/ 5/24	16 4	0 22	0 28	Autoclaved diet eleventh day
2/ 9/24	8 4	0 04	0 11	Autoclaved diet fifteenth day
2/12/24	8 3	0 11	0 18	Autoclaved diet eighteenth day
2/16/24 (5 hours)	10 2	0 12	0 18	Autoclaved diet twenty-second day
2/18/24 (5 hours)	6 4	0	0 08	Autoclaved diet twenty-fourth day
2/23/24 (6 hours)	18 8	0 14	0 20	Autoclaved diet twenty-ninth day
2/24/24 (6 hours)	12 9	0 10	0 17	Autoclaved diet thirtieth day
2/25/24 (5 hours)	11 5	0 17	0 28	Autoclaved diet thirty-first day
2/29/24				Very weak, died in afternoon

TABLE 2—*Effect of Diet Autoclaved with Alkali on Gastric Secretion of Dog (Experiment 27)*

Date	Volume in C c for Five Hours	Average Free Acidity, per Cent Hydro- chloric Acid	Average Total Acidity, per Cent Hydro- chloric Acid	Remarks
3/ 1/24	12 3	0 17	0 23	Fresh diet
3/ 2/24	20 9	0 23	0 28	Fresh diet
3/ 3/24	18 5	0 27	0 32	Fresh diet
3/ 4/24	20 0	0 25	0 29	Fresh diet
3/ 9/24	13 5	0 24	0 30	Fresh diet
3/16/24	14 7	0 21	0 25	Autoclaved diet second day
3/19/24	16 0	0 32	0 39	Autoclaved diet fifth day
3/22/24	16 4	0 35	0 41	Autoclaved diet eighth day
3/25/24	16 6	0 34	0 35	Autoclaved diet eleventh day
3/27/24	18 3	0 31	0 36	Autoclaved diet thirteenth day
3/31/24	19 0	0 26	0 30	Autoclaved diet seventeenth day
4/ 1/24	16 7	0 27	0 31	Autoclaved diet eighteenth day
4/ 4/24	13 0	0 18	0 26	Autoclaved diet twenty-first day
4/ 5/24	15 6	0 21	0 29	Autoclaved diet twenty-second day
4/ 6/24	9 7	0 13	0 19	Autoclaved diet twenty-third day
4/ 9/24 (8 hours)	9 6	0 08	0 16	Autoclaved diet twenty-sixth day
4/15/24	1 1	0	0	Autoclaved diet thirty-second day
4/16/24 (6 hours)	2 0	0 10	0 21	Autoclaved diet thirty-third day
4/20/24				Stiff legged and dizzy, dead thirty-seventh day

TABLE 3—*Effect of (1) Fresh Diet, (2) a Diet Autoclaved with Alkali, (3) Fresh Diet, (4) a Diet Autoclaved with No Alkali, and (5) Fresh Diet on Gastric Secretion of Dog (Experiment 23)*

Date	Volume in C c for Four Hours	Average Free Acidity, per Cent Hydro- chloric Acid	Average Total Acidity, per Cent Hydro- chloric Acid	Remarks
2/ 3/24	36 6	0 25	0 28	Fresh diet
2/ 9/24	36 0	0 29	0 33	Fresh diet
2/12/24	36 5	0 31	0 34	Fresh diet
2/23/24	29 8	0 15	0 22	Autoclaved diet (alkali) eighth day
3/ 4/24	24 2	0 14	0 21	Autoclaved diet eighteenth day
3/10/24	17 2	0 06	0 16	Autoclaved diet twenty-fourth day
3/15/24	24 7	0 16	0 26	Autoclaved diet twenty-ninth day
3/16/24	25 2	0 15	0 22	Autoclaved diet thirtieth day
3/22/24				Pronounced symptoms of beriberi
3/22/24	11 3	0 13	0 19	Fresh diet third day
4/ 6/24	20 4	0 21	0 26	Fresh diet eighteenth day
4/30/24	27 8	0 31	0 37	Fresh diet forty-first day
5/21/24	24 2	0 25	0 31	Fresh diet sixty-fourth day
6/ 2/24	29 9	0 25	0 31	Fresh diet seventy-sixth day
6/14/24	14 2	0 22	0 28	Autoclaved diet (no alkali) twelfth day
6/28/24	15 9	0 21	0 27	Autoclaved diet twenty-sixth day
7/ 9/24	11 4	0 18	0 24	Autoclaved diet thirty-seventh day
7/25/24	11 3	0 18	0 22	Autoclaved diet fifty-third day
8/15/24	8 2	0 19	0 24	Autoclaved diet seventy-fourth day
8/28/24	12 1	0 19	0 22	Autoclaved diet eighty-seventh day
9/ 7/24	21 7	0 33	0 38	Autoclaved diet ninety-seventh day
9/15/24				Mild symptoms of beriberi, no appetite one hundred and fifth day
9/20/24	15 4	0 17	0 20	Fresh diet fifth day
9/21/24	16 6	0 25	0 30	Fresh diet sixth day

neuritic condition, it nevertheless required 105 days to reproduce the obvious symptoms of beriberi. The gastric secretion during this fourth experimental period fluctuated considerably both in volume and in acidity, but the tendency was on the whole toward a decreased total secretion of acid.

TABLE 4—*Effect of Autoclaved Diet on Response to Histamine Hydrochlorid Stimulation of Gastric Secretion (Experiment 43)*

Date	Volume in Cc First Hour	Free Acidity, per Cent Hydro- chloric Acid	Total Acidity, per Cent Hydro- chloric Acid	Remarks
7/26/24	11.5	0.37	0.46	1 mg of histamine hydrochlorid, fresh diet
7/28/24	3.1	0.25	0.34	0.5 mg of histamine hydrochlorid, fresh diet
7/29/24	1.0	0	0.08	0.1 mg of histamine hydrochlorid, fresh diet, no mucus
7/30/24	1.5	0	0.05	0.1 mg of histamine hydrochlorid, fresh diet, watery
7/31/24	1.8	0	0.06	0.1 mg of histamine hydrochlorid, fresh diet, watery
8/ 2/24	8.0	0.20	0.35	0.4 mg of histamine hydrochlorid, fresh diet
8/ 5/24	2.1	0	0.07	0.1 mg of histamine hydrochlorid fourth day, autoclaved diet, mostly mucus
8/15/24	1.0	0.02	0.16	0.1 mg of histamine hydrochlorid fourteenth day, autoclaved diet
8/21/24	1.0	0	0.05	0.1 mg of histamine hydrochlorid twentieth day, autoclaved diet, mostly mucus
	2.0	0.06	0.16	0.15 mg of histamine hydrochlorid twentieth day, autoclaved diet
8/22/24	5.0	0.06	0.33	0.4 mg of histamine hydrochlorid twenty first day, autoclaved diet
8/28/24	1.1	0.05	0.20	0.15 mg of histamine hydrochlorid twenty- seventh day, autoclaved diet
8/29/24	4.0	0.30	0.46	0.60 mg of histamine hydrochlorid twent eighth day, autoclaved diet
8/31/24	2.5	0.03	0.16	0.15 gm of histamine hydrochlorid thirtieth day, autoclaved diet
9/ 1/24	1.5	0.24	0.28	0.60 mg of histamine hydrochlorid thirty first day, autoclaved diet
9/ 2/24				Died, slight symptoms of beriberi

TABLE 5—*Effect of Autoclaved Diet on Response to Histamine Hydrochlorid Stimulation of Gastric Secretion in Dog (Experiment 48)*

Date	Volume in Cc First Hour	Free Acidity, per Cent Hydro- chloric Acid	Total Acidity, per Cent Hydro- chloric Acid	Remarks
8/26/24	3.5	0.13	0.25	0.1 mg of histamine hydrochlorid, fresh diet
	10.5	0.34	0.40	0.4 mg of histamine hydrochlorid, fresh diet
8/29/24	2.5	0.10	0.18	0.05 mg of histamine hydrochlorid, fresh diet
	4.5	0.22	0.30	0.2 mg of histamine hydrochlorid, fresh diet
8/29/24	2.5	0	0.08	0.05 mg of histamine hydrochlorid, fresh diet
	3.7	0.13	0.22	0.2 mg of histamine hydrochlorid, fresh diet
9/ 6/24	3.7	0	0.04	0.05 mg of histamine hydrochlorid, auto claved diet eighth day
	3.0	0.01	0.08	0.1 mg of histamine hydrochlorid, auto claved diet eighth day
9/20/24	5.5	0.03	0.20	0.15 mg of histamine hydrochlorid, auto- claved diet twenty second day
	3.5	0	0.08	0.1 mg of histamine hydrochlorid, auto- claved diet twenty second day
9/21/24	4.0	0.13	0.25	0.6 mg of histamine hydrochlorid, auto- claved diet twenty third day
9/25/24				Discontinued the experiment

Tables 4 and 5 show that the gastric secreting mechanism becomes more refractory as polyneuritis develops in the dog. Thus it required from one and one-half to three times as great histamin doses to bring about a certain maximum secretion of acidity in the last stages of beriberi as in the normal control period.

Table 6 gives the results of similar experiments following the injection of gastrin. Although there appears to be a slight indication of decreased response to gastrin injection as beriberi develops, nevertheless the proportional change is not as great as after the stimulation by a meal or by histamin.

TABLE 6—*Effect of Autoclaved Diet on Response to Gastrin Stimulation in Dog*

Date	Volume in C c First Hour	Free Acidity, per Cent Hydro- chloric Acid	Total Acidity, per Cent Hydro- chloric Acid	Remarks
Experiment 24				
2/ 4/24	5.3	0.33	0.41	1 c c of gastrin, fresh diet
2/11/24	3.8	0.33	0.44	1 c c of gastrin, fresh diet
2/13/24	4.3	0.25	0.34	1 c c of gastrin, fresh diet
3/ 5/24	1.9	0.27	0.37	1 c c of gastrin, autoclaved diet fifth day
3/12/24	2.0	0.15	0.26	1 c c of gastrin, autoclaved diet twelfth day
3/29/24	4.7	0.28	0.33	1 c c of gastrin, autoclaved diet twenty-ninth day
4/ 2/24				Died of beriberi
Experiment 27				
3/ 5/24	5.2	0.33	0.40	1 c c of gastrin, fresh diet
3/12/24	5.5	0.27	0.33	1 c c of gastrin, fresh diet
3/29/24	5.4	0.35	0.40	1 c c of gastrin, autoclaved diet fifteenth day
4/14/24	6.6	0.37	0.43	1 c c of gastrin, autoclaved diet thirty first day
4/16/24	1.3	0.17	0.25	1 c c of gastrin, autoclaved diet thirty third day, symptoms of beriberi
4/20/24				Died thirty-seventh day

TABLE 7—*Effect of Addition of Yeast Vitamin to Diet Autoclaved with Alkali on Gastric Secretion of Dog (Experiment 42)*

Date	Volume in C c for Four Hours	Average Free Acidity, per Cent Hydro- chloric Acid	Average Total Acidity, per Cent Hydro- chloric Acid	Remarks
7/23/24	4.3	0.05	0.13	Fresh diet, good health
7/25/24	3.5	0.04	0.07	Fresh diet, good health
7/27/24	3.6	0.01	0.04	Fresh diet, good health
8/ 2/24	4.1	0.06	0.11	Autoclaved diet plus vitamin, good health sixth day
8/15/24	4.3	0.12	0.22	Autoclaved diet plus vitamin, good health nineteenth day
8/22/24	3.8	0.07	0.12	Autoclaved diet plus vitamin, good health twenty sixth day
9/ 1/24	6.7	0.22	0.30	Autoclaved diet plus vitamin, good health thirty-sixth day
9/ 7/24	6.6	0.09	0.15	Autoclaved diet plus vitamin, good health forty-second day
9/21/24	3.6	0.01	0.07	Autoclaved diet plus vitamin, good health fifty-sixth day
9/25/24				Good health, discontinued the experiment

Table 7 shows that the addition of Harris yeast vitamin to an alkali autoclaved diet keeps a dog in good condition for some fifty-six days and that the gastric secretion appears to remain normal. The dog used for this experiment was, however, a rather poor secretor. Nevertheless, the good health of the animal proves that in the alkaline autoclaving process the destructive action does not reside in the racemization of the proteins but in the main in destruction of the vitamin. Table 7 simply shows that Harris yeast vitamin does not contain a "gastric secretin" activity similar to that of histamin or of gastrin.

TABLE 8—*Effect of Injection of Harris Yeast Vitamin Preparation on Gastric Secretion of Dog*

Experiment	Date	Volume Above Continuous Secretion	Free Acidity, per Cent Hydrochloric Acid	Total Acidity, per Cent Hydrochloric Acid	Remarks
27	4/16/24	0	—	—	1 tablet injected, sick with beriberi
24	4/ 2/24	0	—	—	1 tablet injected, sick with beriberi
23	4/ 8/24	0	0	0.06	1 tablet injected, recovered from beriberi
28	4/ 8/24	0.1	0	0.03	1 tablet injected, fresh diet
	4/16/24	0	0	0.03	1 tablet injected, fresh diet

CONCLUSIONS

1 Feeding a beriberi producing diet to a dog gradually decreases the total volume as well as the free and the total acidity of gastric secretion

2 The gastric secretory mechanism of the beriberi dog is not only less responsive to the partaking of food but it is also appreciably more refractive toward histamin hydrochlorid injection. The gastric response after gastrin injection is modified only slightly if at all

3 The harmful effect of alkali in the autoclaving process is not due to racemization of the proteins but to destruction of the antineuritic vitamin

4 The antineuritic vitamin is not a gastric secretagogue

THE HEALING OF GASTRIC ULCERS *

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In a previous article ¹ we reported a series of ulcer cases which under medical treatment showed relief of symptoms. When these cases were checked by repeated roentgen-ray examinations, a number of patients showed a gradual diminution and a final disappearance of the ulcer niche. Since the roentgen-ray reports corresponded so closely with the patients' improved clinical condition, we felt that this was strongly suggestive of the healing of the ulcer. Especially was this true in patients who were under 45 years of age and who had had short periods of active symptoms. In specimens resected at operation we were able to show by both gross and microscopic methods several cases of healing of duodenal ulcer. In six cases in which a subtotal gastrectomy had been performed a few weeks after hemorrhage, a healed duodenal ulcer was found in the specimens removed at operation. We were not fortunate enough to obtain specimens that showed convincingly a similar process of healing in ulcers of the body of the stomach. However, as a result of our observations during the last year, we are now able to state that in certain types of gastric ulcer, a like process of healing also takes place following the institution of medical treatment. The proof of the healing of such ulcers consists in the improvement of clinical symptoms, marked diminution in size of the niche, and the corresponding ocular evidence of healing in the specimen removed at the operating table.

REPORT OF CASES

CASE 1—A man, aged 39, a painter by occupation, with a previous history of arrested pulmonary tuberculosis, had gastric symptoms which began four years before admission with epigastric pain, cramplike in character, occurring at irregular periods after meals. Roentgenographic examination at this point showed a penetrating ulcer of the lesser curvature. The patient was referred to the hospital for medical treatment.

After six weeks reexamination by the roentgenographic method showed a disappearance of the niche.

After this treatment the patient remained well for approximately two years, when he returned with recurrent symptoms, characterized by cramplike pain, sour eructations and vomiting of food, followed by relief of the pain. Roentgen-ray examination showed a small penetrating ulcer at the reentrant angle of

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1 Crohn, B. B., Weiskopf, Samuel, and Aschner, P. W. The Life Cycle of Peptic Ulcer, *Arch. Int. Med.* **35** 405 (April) 1925.

the stomach. After two weeks of conservative medical treatment in the hospital the gastric symptoms disappeared, and examination a few weeks later showed the disappearance of the niche.

For six months he felt well, but returned at the end of that period, again with recurrent symptoms. Another roentgen-ray examination showed a reappearance of the niche at the same site, just above the reentrant angle. The patient was now determined to undergo a radical surgical treatment for the removal of his recurrent ulcer. As his general condition was not satisfactory we determined to institute a preliminary course of medical treatment hoping to improve his strength and nutrition, and incidentally to utilize the opportunity to observe the effects of conservative therapy on the course of a recurrent ulcer. After three weeks of such treatment, the symptoms were considerably relieved, vomiting was allayed and the general condition of the patient was better.

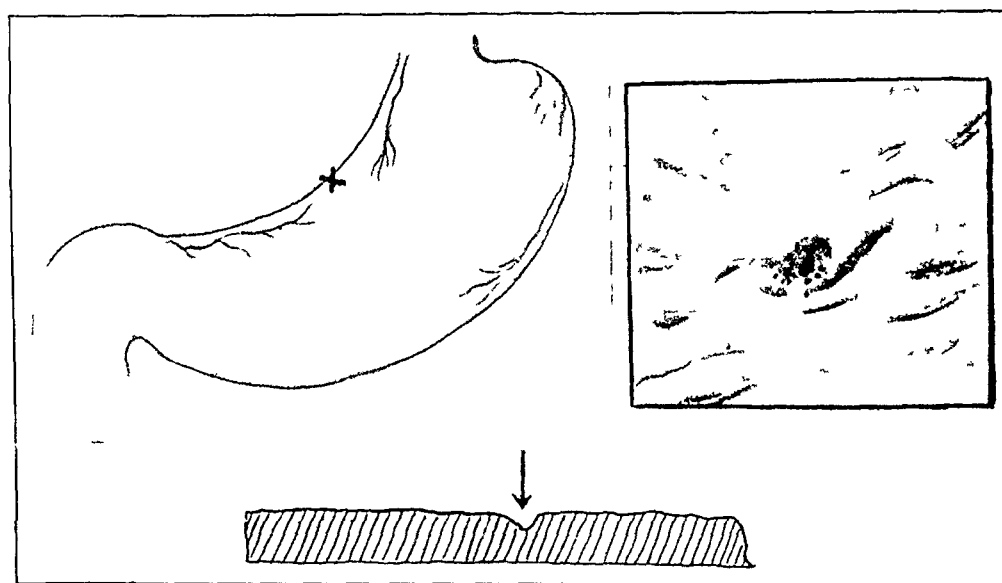


Fig 1 (Case 1)—Cross section of healing ulcer as removed at operation, shallow depression remaining after healing was almost completed

A subtotal gastrectomy was then performed by Dr A A Berg, the specimen removed (Fig 1) showed an ulcer in the advanced stages of healing. A small depression about 3 by 4 mm in diameter and about 0.5 mm in depth represented the remains of an ulcer, on palpation there was found to be practically no induration about the lesion. Microscopic section showed the ulcer filled with granulation tissue proceeding from the edges and the base, there was slight edema in the neighborhood of the defect, and some infiltration with round and plasma cells. The sides were contracted until only a small dimple or depression remained as the residuum of the previous ulcer, the defect itself occupying an area corresponding to one microscopic field (low power). The base of the defect was formed by hyaline and somewhat degenerated fibromuscular tissue. Evidently the process of healing, though far advanced, had not yet been carried to the point of epithelialization of complete healing.

CASE 2—A woman, aged 39, fifteen years before admission had suffered with a gastric disturbance for which a cholecystectomy had been performed. An interval of six years followed during which the patient was entirely free from symptoms. At the end of this period epigastric pain recurred about one-half hour after eating. These symptoms lasted from two to three weeks following which another period of freedom of symptoms ensued. During the last eight

years such attacks recurred once or twice a year, each attack lasting from two to four weeks and being followed by a free interval of several months. In the last year her attacks recurred with greater frequency and were longer, thus allowing a shorter interval of freedom of symptoms. In the last two months, during which time she came under the observation of one of us, she had been suffering from continuous symptoms, consisting of postprandial cramplike pain, vomiting and marked loss of weight and strength. Roentgen-ray examination showed a large penetrating niche at the lesser curvature, above the recntrant angle.

In view of the long history with constantly recurring symptoms, particularly the severity of the last attack, it was deemed advisable to urge operation. Here again a preliminary course of medical nutrition and strength seemed indicated, the purpose being to improve the general nutrition and strength and to allay the severity of the symptoms, so as to make her a less dangerous surgical risk. After three weeks of such treatment the patient's symptoms were considerably alleviated. At this point a roentgen-ray examination showed an almost complete disap-

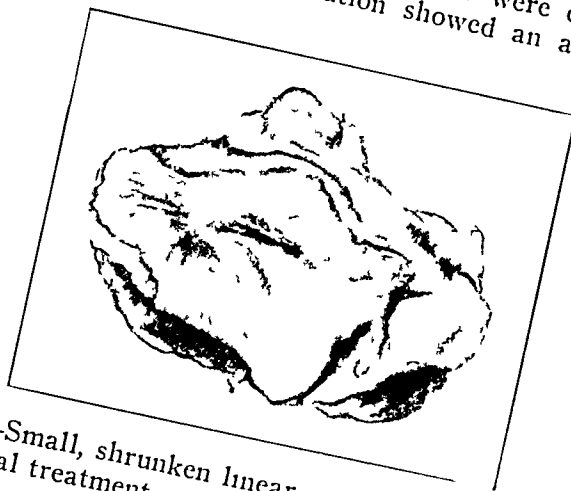


Fig 2 (Case 2)—Small, shrunken linear scar of penetrating ulcer remaining after course of medical treatment, specimen was excised at operation

pearance of the previously observed niche. Nevertheless, in view of the past history of repeated severe attacks the original intention of urging operation was adhered to. An excision of the ulcer, with gastro-enterostomy, was performed by Dr L. M. Kahn at the Lebanon Hospital.

The excised specimen (Fig 2) showed a linear contracted depression at the site of the previously observed niche, approximately from 6 to 8 mm in length, about 2 mm broad, and so superficial in depth that it was almost flush with the surface of the mucous membrane of the stomach, the lateral longitudinal walls being drawn together so as to leave only a linear slit. Microscopic examination of the section through the lesion showed the gastric mucous membrane the seat of a chronic inflammatory lesion with numerous capillaries and round and plasma cells between the glandular acini. One small area of the mucosa presented a mass of granulation tissue (the site of the previous ulcer) the surface of which was partially necrotic (Fig 3). The central area of the surface was still covered by a thin layer of necrotic membrane. From the sides of the ulcer epithelium with distinct, rather large irregular glandular acini was apparent growing in from both sides.

HISTOLOGIC EVIDENCE OF HEALING

The examination of tissue of these specimens furnished evidence of the method of the reparative process by which at least some ulcers undergo healing under conservative treatment. We find in these ulcer

specimens evidences of healing in successive stages, such as are ably described by Bolton² and again more recently in the more exact microscopic studies of Ashkanazy³ and Perman⁴ The essential process of healing seems to consist of the filling of the crater by the growth of firm granulation tissue from the sides and the base of the ulcer, by the linear retractions of the sides of the ulcer with the approximation of the lateral surfaces (as better demonstrated in our second specimen), and by the ingrowth of newly formed epithelial tissue from the sides of the wound



Fig 3 (Case 2)—Specimen in Figure 2 showing ulcer defect replaced by granulation tissue, new epithelium growing in from both sides and attempting to cover over necrotic membrane that remains on surface of previous ulcer, newly formed blood vessels entering granulation area, muscularis mucosa absent having been destroyed in ulceration process and not being capable of regeneration

toward the center This regenerating epithelial tissue advances from the sides of the healing ulcer as a thin line of columnar epithelial cells showing at the more distal portion, nearer the sides of the ulcer an increasing tendency to regenerate acini and to form new immature and irregular gastric glands A definite characteristic in this healing process is the inability to regenerate the portion of muscularis mucosa

2 Bolton *Ulcer of the Stomach*, London, 1913

3 Ashkanazy *Virchows Arch f path Anat* **234** 111, 1921

4 Perman *Acta Scandinav Chir* **55** 286, 1923

destroyed in the course of ulcer. A cross section of such healing ulcer shows the frayed ends of the muscularis mucosa buried in the newly formed granulative tissue.

CORRELATION OF HISTOLOGIC PROCESS OF HEALING WITH CLINICAL AND ROENTGENOGRAPHIC MANIFESTATIONS

In both these cases we have seen that the process of healing marches hand in hand with the regression of the subjective clinical symptoms and the objective evidence of the subsidence of the niche formation in the roentgenogram. It is to be regretted that in the first case cited we failed to obtain a second roentgenographic examination after the institution of a course of medical treatment, this lapse we corrected in our second case by obtaining a roentgen-ray examination immediately before operation and directly after three weeks of medical treatment. The marked diminution in the size of the niche, amounting almost to disappearance, corresponds to the advanced stage of healing evidenced by the specimen in Figure 3.

TYPES OF ULCER IN WHICH HEALING MAY BE ANTICIPATED

We are inclined to accept the classification of gastric ulcers outlined by Sherren.⁵ He groups all ulcers as (1) acute, (2) recurrent acute and (3) chronic ulcers. He states quite clearly, as Bolton does also, that acute ulcers most often heal spontaneously on medical treatment. Recurrent acute ulcers, he defines as ulcers in which the onset is sudden, with a short course of clinical symptoms followed by an intermission period of variable length, this cycle tends to recur an indefinite number of times. In the latter type of ulcer, Sherren believes that spontaneous healing in the intermission takes place. In the "chronic" type of ulcer, however, the onset is gradual, symptoms almost continuous, and the chances of spontaneous cure under conservative treatment are rather poor. In a twenty-two year follow-up of a series of cases carried out by Nielsen,⁶ he was able to show lasting cure in 60 per cent of what we would term the acute and the recurrent acute type of ulcer, while in the chronic group of ulcers, healing took place in only 9 per cent of the cases. These ideas and conclusions bear considerable confirmatory evidence on the observations we have made. We feel that we have added the pathologic evidence necessary to the statement that both acute and recurrent acute ulcers can and do heal in the intermission period. Our clinical observations are substantiated by the roentgen-ray evidence of the disappearance of the niche and both facts are amply strengthened by the gross and histologic demonstrations of the reparative process that takes place in such ulcers during the institution of medical treatment.

5 Sherren. *Lancet*, March 8, 1924, p. 1477.

6 Nielsen. *Acta Med Scandinav* 58:286, 1923.

The durability of the healing process is unfortunately problematic. In a fair percentage of cases the healing may be permanent and the clinical symptoms fail to recur. In probably a larger proportion of cases the healing process is incomplete and a tendency to the relapse of the ulcer and of the clinical symptoms is only too often the fact.

UTILIZATION OF PHASE OF HEALING IN INTERPRETATION OF
SOME OF MORE OBSCURE TYPES OF GASTRIC CASES

So-called "essential hematemesis" remains one of the questions of medicine today. Clinicians who have thought much on this subject are divided into two schools: (1) those who think that there is always an acute ulcer or erosion (Dieulafoy erosion) as the cause of such bleeding, and (2) those who believe that the gastric mucosa is capable of an essential profuse hemorrhage without a demonstrable organic lesion. (We are excluding from this discussion those cases of gastric hemorrhage in which a hemorrhagic diathesis, purpura, leukemia, Banti's disease or a portal cirrhosis is present to account for the symptoms.)

By observing several of these so-called "essential hematemesis" cases over a course of years, having the advantage of seeing such patients on repeated admissions to the wards or in the outpatient department, certain facts have impressed themselves. We shall not go into a detailed description of the cases which are included in a paper to be published by Stenbuck,⁷ in which this subject is fully described and discussed, but we wish to refer to instances in which hematemesis has taken place without previous gastric symptoms. At roentgen-ray examination after the shock of the hemorrhage had passed off, that is, a few weeks later, no organic gastroduodenal lesion could be demonstrated. Cases explored at this moment usually failed to show a lesion. When such cases are followed over a course of years, it has been a not infrequent experience to observe that at some future date the full syndrome of a gastro-intestinal ulceration will occur. If the patient is operated on now, a typical gastric or duodenal ulcer may be found. In this way several cases that we have regarded for years as cases of essential hematemesis have eventually declared themselves as cases of ulcer and a subtotal gastrectomy has placed in our hands a typical ulcer specimen.

One is at a loss to explain why roentgenographic examination and exploratory operation soon after the hemorrhage failed to discover a lesion, for it is on this negative finding that the designation of essential hematemesis has been created. We believe that this explanation lies in the fact that the hematemesis was caused by an acute ulcer, probably not an erosion but a rapidly forming callous ulcer, that between the time of the hemorrhage and the time of the roentgen-ray examination

⁷ Stenbuck, J. To be published.

or exploratory laparotomy the ulcer had partially healed over, defying detection. Since last year we were able to demonstrate six cases of duodenal ulcer that had healed within a few weeks of hemorrhage, we would suggest this explanation as a possible hypothesis to explain the nature of at least some of the cases of "essential hematemesis." With the later recurrence of symptoms the opportunity was placed within our grasp of defining the true nature of the malady as that of peptic ulcer.

Similarly we are often placed in a difficult position to explain the negative findings at an exploratory laparotomy, in cases in which a clear-cut and suggestive history exists, if not a positive roentgenographic examination. It has been our good fortune on several occasions to follow the course of such cases over a period of years and to discover that after a latent period the patient returns with symptoms quite typical of ulcer and a positive roentgenographic examination. An operation performed now yields a positive finding, usually a typically indurated duodenal ulcer.

This experience has repeated itself so often that we feel that the lack of positive findings at the first operation should not merely be ascribed to the shortcomings of the surgeon in palpating the stomach and duodenum in the opened abdomen or to the technical difficulties of demonstrating a small ulceration at such a time. Of late surgeons have not hesitated to incise the stomach or duodenum and carefully to examine the mucosa in an effort to find an ulceration that defies palpation. In this class of case, we feel that the first exploratory operation is performed in a phase of the disease in which the ulcer has undergone regression and temporary healing, while the second exploratory operation is done at a more fortuitous time and discovers the real nature of the disease to be that of ulceration.

We offer this as a hypothesis as to the nature of some of the negative exploratory operations, and feel that the subsequent discovery of an ulcer is to be explained on the basis that these are all variations in the course of the life cycle of ulcer.

SUMMARY

1 In two cases in which partial gastrectomy was performed for gastric ulcer, operation was timed to take place at the end of a course of preliminary medical treatment. The specimens removed showed these ulcers in the last stage of healing. In one case, roentgen-ray examination just before operation showed the disappearance of the niche that had been present.

2 So-called "essential gastric hemorrhage" cases, if operated on soon after the hemorrhage, may show negative findings, if followed over a course of years they may eventually be demonstrated to be true ulcer.

cases It is suggested that the negative findings at the first operation are due to the rapid healing of the ulcer after hemorrhage

3 The rapid regression of ulcers in the intermission period will explain many of our cases of negative finding at exploratory laparotomy in cases with a suggestive ulcer history In a series of such cases in which operation was done at a later date during a recurrence of the symptoms, the patient showed definite ulcer

4 The failure to demonstrate the lesion of a gastric or duodenal ulcer at exploratory laparotomy may therefore be due, at times to the fact that the operation is carried out at a period in the life cycle of an acute ulcer when rapid regression and healing have obliterated the ulcer crater and made the lesion impossible of discernment

ACUTE MERCURIC CHLORID POISONING [†]

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The usual sequence of events following ingestion of lethal doses of mercuric chlorid has become all too familiar in the last ten years. Initially there are abdominal cramps and distress, often with bloody vomitus, diarrhea and melena may follow, and an acute tubular nephritis often supervenes with rapidly developing anuria and death in uremia in from three to twenty days. It has occasionally been noted that the course may be more rapid. Kaufmann ¹ cites a case of death with subnormal temperature on the second day. Zangger ² mentions the possibility of early death as do Oliver, ³ Starkenstein ⁴ and Cushny, ⁵ and Burmeister and McNally ⁶ have evidently observed such cases though they give no details of them. Fussell ⁷ saw death within twelve hours, Weiss ⁸ observed death nineteen hours after poisoning and Vaughan ⁹ states that death may take place in thirty minutes. His description of acute collapse terminating fatally in from twelve to fourteen hours as the common clinical picture is contradicted by the majority of recent observers. Lambert and Patterson, ¹⁰ Gatewood and Byfield, ¹¹ Foster, ¹² Achard, ¹³ as

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1 Kaufmann, Eduard. Neuer Beitrag zur Sublimatintoxication nebst Bemerkung über die Sublimatniere, Virchows Arch f path Anat **117** 227 (Aug) 1889

2 Zangger, H. Die anorganischen Gifte, in Mohr, L., and Staehelen, R. Handbuch der Innere Medizin, Berlin, 1919, **6** 588

3 Oliver, Thomas. Metallic and Some Other Forms of Poisoning, in Albutt, Clifford, and Rolleston, H D. A System of Medicine, London, 1912, **2** 1007

4 Starkenstein, Emil. Die anorganischen Gifte, in Kraus, F., and Brugsch, T. Spezielle Pathologie u Therapie innerer Krankheiten, Berlin, 1913, **9** 1014

5 Cushny, A R. A Textbook of Pharmacology and Therapeutics, Ed 7, Philadelphia, 1918, p 625

6 Burmeister, W H., and McNally, W D. Acute Mercury Poisoning, J M Res **31** 85 (March) 1917

7 Fussell, M H. In Lambert, S W., and Patterson, H S. Poisoning by Bichlorid of Mercury and Its Treatment, Tr A Am Phys **30** 282, 1915

8 Weiss, H B. Mercuric Chlorid Poisoning, Arch Int Med **33** 224 (Feb) 1924

9 Vaughan, V C. Toxicology, in Forchheimer. Therapeutics of Internal Diseases, Ed 2, New York, 1916, **1**.

10 Lambert, S W., and Patterson, H S. Poisoning by Mercuric Chlorid and Its Treatment, Arch Int Med **16** 865 (Nov) 1915

11 Gatewood, L C., and Byfield, A F. A Clinical Report on Acute Cases of Mercuric Chlorid Poisoning, Arch Int Med **32** 456 (Sept) 1923

12 Foster, N B. Mercury Nephritis, Arch Int Med **15** 754 (May) 1915

13 Achard, C. Empoisonnement par le Sublime, Paris med **45** 33 (July) 1922. Achard, C., and Rouillard, J. Forme Benigne de l'Intoxication par le Sublime, La Medecine **4** 444 (March) 1923

well as by the data of Franz,¹⁴ in whose series of 101 compiled cases with fifty-eight fatalities only one occurred early, although the doses taken were in several cases enormous (from 5 to 10 gm)

During the years 1923 and 1924, in a series of cases of mercuric chlorid poisoning treated in the medical clinic of Johns Hopkins Hospital, the possibility of early death was brought forcibly to mind. Two of the cases will be given in detail.

REPORT OF CASES

CASE 1—History—M W, a white married woman, aged 20, a factory worker, was admitted through the accident room at 9 30 p m, May 18, 1924, complaining of having swallowed mercuric chlorid. In the history, there were suggestive psychotic data concerning a sister. Her general health had been good. There was an indefinite story of occasional edema of the ankles and periorbital regions for two years, and she had had nocturia for three years intermittently. She had had sore throat frequently but no recognized nephritis. For one and one-half years she had had leukorrhea. She had been married three years, there were two healthy children and no miscarriages recorded.

At 8 p m, May 18, 1924, she swallowed two 7½ grain (0.49 gm) tablets of mercuric chlorid. Whether or not she had had supper could not be ascertained. Almost immediately she vomited a brownish fluid, fifteen minutes later she was given two glasses of milk and promptly vomited them, with no accompanying blood. At 9 15 p m she was brought to the hospital. In the accident room she was given copious gastric lavage with milk and eggs, and 40 gm of sodium thiosulphate was introduced into the stomach by tube. Some of this was vomited but the larger part was retained.

Physical Examination—At 9 30 p m on admission to the ward, she was moderately shocked, but the examination was otherwise negative save for marked pyorrhea alveolaris, a heart at the upper limits of normal size, a tender mass in the right pelvis and a suggestion of pretibial edema. The blood pressure was 118 systolic, 84 diastolic.

Blood examination, the following morning revealed hemoglobin (Sahli), 90 per cent, red blood cells, 4,860,000, white blood cells, 34,680, a smear not unusual except for 90 per cent of polymorphonuclear neutrophils in the differential count. Blood drawn immediately after death at 12 40 a m, May 20, by cardiac puncture, showed nonprotein nitrogen, 98.1 mg, creatinin, 2.97 mg, and chlorids, 420 mg. The blood Wassermann reaction was negative. Urine voided the morning of May 19 was turbid, of 1.020 specific gravity, acid, contained a heavy cloud of albumin (++) , no sugar, numerous red and white blood cells and hyaline and cellular casts. The stools were bloody and mucopurulent.

Treatment and Course—Soon after the patient reached the ward, 15 gm of sodium thiosulphate was given intravenously, and the drug was further given intravenously in 1 and 15 gm dosage at 8 a m and 6 p m, May 19. A solution of 0.8 per cent each of potassium acetate and sodium thiosulphate was given continuously by rectal drip method, and 200 cc of milk with 4 gm of sodium thiosulphate or an equal amount of potus imperialis was given by mouth at alternate hours. The afternoon of May 19, 5,000 cc of physiologic sodium chlorid solution was given by subpectoral infusion. High colonic irrigations with 0.4 per cent of sodium thiosulphate solution were undertaken and potassium chlorate mouth wash was used frequently. A total of 40 gm

¹⁴ Franz, F. Die im Deutschen Reich während der Jahre 1897-1905 amtlich gemeldeten Vergiftungen mit Sublimat, Arb a d k Gsmdhsamte 34 1 (March) 1910.

of sodium thiosulphate was given by mouth after the patient reached the ward. During the first night in the ward, the patient vomited frequently and was incontinent of urine. The passage of urine was not observed after 10 a m, May 19. The vomiting had ceased, she was less shocked and took fluids well by mouth, but she was rather dulled mentally in the afternoon and in the evening developed active delirium and pulled out the subpectoral needle. At 11 p m she suddenly became cyanosed, her breathing was slow and shallow and her extremities were cold. In spite of caffeine sodium benzoate and strophanthin subcutaneously and intramuscularly, she became comatose, her pulse weakened, she developed Cheyne-Stokes breathing and the heart stopped at 12 40 a m, May 20. Intracardiac epinephrin had no effect. Necropsy was refused.

CASE 2—History—M J J, a white married woman, aged 35, was admitted through the accident room, May 20, 1924, at 12 30 p m, complaining of having swallowed mercuric chlorid. For several years she had had occasional swelling of the ankles and transient edema beneath the eyes, for a similar period she had had occasional nocturia. The tubes and ovaries were said to have been removed two years before. Otherwise, the history was negative. Of three pregnancies, one was a miscarriage, two children were living and well.

At 8 a m the morning of admission, she had eaten an egg, bacon, bread and coffee. At 10 30 a m she swallowed four $7\frac{1}{2}$ grain (0.49 gm) tablets of mercuric chlorid. Almost immediately she was given milk by mouth, and vomiting ensued, the vomitus was bluish but contained no particles of tablets. At 12 15 p m she came to the accident room where copious gastric lavage was instituted and 3 gm of sodium thiosulphate was left in the stomach.

Physical Examination—At 12 30 p m, on admission to the ward, she was somewhat dazed and complained of pain in the throat and stomach. She was vomiting small quantities of fluid with which were mixed shreds of mucus, bits of tissue that were apparently gastric mucosa, and small quantities of blood. She presented exceptionally short arms and legs in relation to trunk length without actually appearing achondroplastic. The examination revealed tenderness in the episternal notch, diffuse abdominal tenderness without spasm and a suggestion of edema of the ankles. Blood examination, at about 2 p m, revealed hemoglobin (Sahli), 65 per cent, red blood cells, 4,120,000, white blood cells, 40,000, a smear not unusual except for 92 per cent of polymorphonuclear neutrophils in the differential leukocyte count. The blood Wassermann reaction was negative. Blood drawn by cardiac puncture immediately after death showed nonprotein nitrogen, 23.3 mg, creatinin, 2 mg, and chlorids, 478 mg. Urine voided soon after reaching the ward was of 1.008 specific gravity, reaction not recorded, albumin ++, no sugar, there were many white blood cells and cellular casts in the sediment but no red blood cells and it gave a negative guaiac test.

Treatment and Course—Within five minutes after the patient reached the ward, she was given 15 gm of sodium thiosulphate intravenously in 50 c c of fluid. Because of the character of the vomitus and the abdominal tenderness, it was considered unwise to force fluids by mouth and provoke further vomiting, a solution of 0.8 per cent each of sodium thiosulphate and potassium acetate was given by rectal drip method, and of this about 600 c c was absorbed. In the early afternoon, 1,100 c c of physiologic sodium chlorid solution was given as a subpectoral infusion. At 4 p m she was given 200 c c of potus imperialis, which she retained, as she did an equal volume of milk with 2 gm of sodium thiosulphate given thirty minutes later. She voided on reaching the ward but not afterward. At 3 p m she was mildly delirious. At 4 p m before she began fluids by mouth, the abdomen was examined and found soft and not tender. At 5 p m, as preparations were being made for a second intravenous injection of sodium thiosulphate, she suddenly collapsed, with cyanosis, shallow breathing,

a slow but thready pulse, profuse sweating and total unresponsiveness, she died within five minutes. Intracardiac epinephrin had no effect.

At necropsy at 9 p. m., May 20, for the record of which I am indebted to Dr. S. M. Seidlin of the Department of Pathology of Johns Hopkins University, the positive gross findings were as follows. The mucosa of the esophagus was slightly congested. The stomach contained 200 c.c. of yellowish, semifluid, coagulated material, the wall was everywhere congested, and there were two areas of necrosis 7 by 4 and 2 by 3 cm. in diameter in the wall, without perforation. The duodenal mucosa was slightly hyperemic, as was that of the cecum. The kidneys weighed 150 and 160 gm., their capsules stripped readily, the surface was smooth and pink. The cortical portion did not appear enlarged or swollen but, in places, rather opaque. The striae were in many places very indistinct, but there were no hemorrhages. There was a cyst in the right broad ligament. The heart, lungs, spleen, liver, suprarenals and marrow appeared normal.

Microscopically, the kidneys showed extensive necrosis of the tubular epithelium with desquamation, this destroyed almost all the convoluted tubules. There was no calcification. The collecting tubules were well preserved, but some were filled with casts. The glomeruli, the capsules, the vessels and the mucosa of the pelves and calices were normal. Dr. Seidlin's impression was that the kidneys had received recent injury but that there was no evidence of active inflammatory change. Sections of the injured stomach wall showed necrosis, edema, congestion of vessels and hemorrhages. The uterine endometrium had the hyperplastic appearance usually seen before menstruation. The broad ligament cyst showed normal ovarian tissue. The heart, liver, spleen, suprarenals, pancreas, thyroid and bone marrow were normal, and the lungs showed edema and thickening of the alveolar walls in some places, and one or two nodules probably representing an old tuberculosis.

The cause of death shortly after mercurial poisoning has been studied in animals without definite conclusions. Von Mering,¹⁵ using subcutaneous dosage, observed sudden collapse and death in an agonal state in several instances. The accompanying fall in blood pressure he showed was not relieved by sectioning the vagi. MacNider¹⁶ found that of a group of dogs who received the drug by stomach, a certain number promptly developed an intense gastro-enteritis and died in collapse and shock with subnormal temperature, cyanosis, shallow breathing, rapid heart action and feeble heart sounds. Salant¹⁷ observed a fall in blood pressure soon after introduction of mercuric chlorid into the duodenum, followed by evidence of cardiac damage, arrhythmia, including complete heart block and circulatory collapse. Lee¹⁸ considers the drug a definite cardiac depressant, and thinks this action probably responsible for early deaths, of which he gives no instances. Cushny³ on the contrary suggests that the fall in blood pressure is probably the result of peripheral

15 Von Mering, J. Ueber die Wirkungen des Quecksilbers auf den thierischen Organismus, *Arch. f. exper. Path. u. Pharmacol.* **13** 86 (Oct.) 1880.

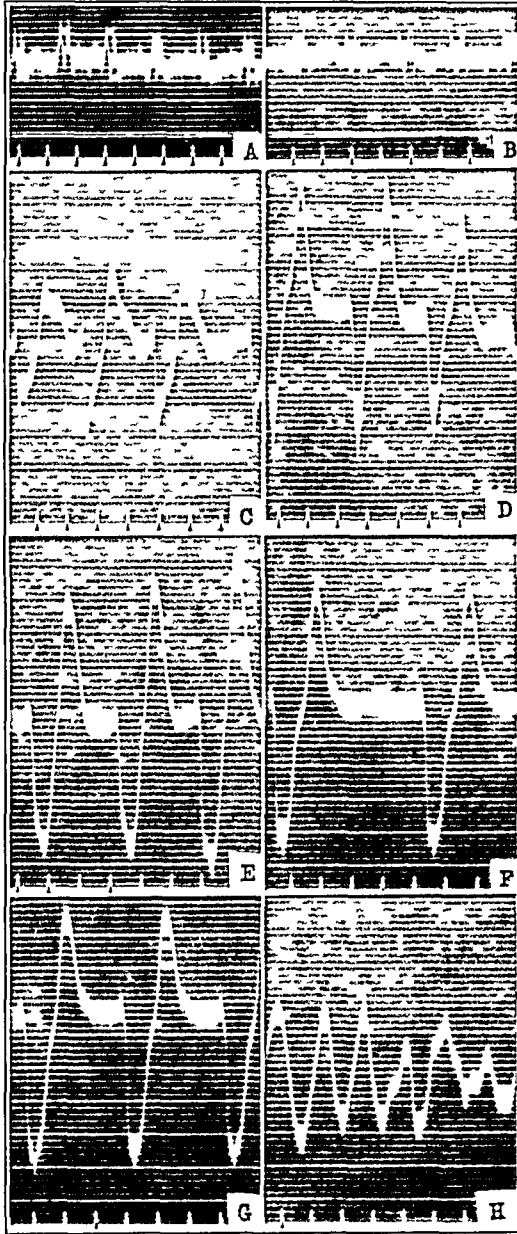
16 MacNider, W. D. A Study of Acute Mercurial Chlorid Intoxication in the Dog with Special Reference to the Kidney Injury, *J. Exper. Med.* **27** 519 (April) 1918.

17 Salant, William. Pharmacology of Mercury, *J. A. M. A.* **79** 2071 (Dec. 16) 1922.

18 Lee, R. V. The Pharmacology of Mercury, *J. A. M. A.* **81** 1748 (Nov. 24) 1923.

small vessel paralysis, together with dilatation of the splanchnic circulation incident to local action of the drug on the gastro-intestinal tract

At the suggestion, and with the aid, of Dr S A Levine, an attempt was made to observe direct action of the drug on the myocardium using the intravenous method in a cat and the string galvanometer as employed



Lead II in etherized cat weighing 27 kg, *A*, control lead, *B*, six minutes after 10 mg of mercuric chlorid intravenously, *C*, four minutes later, total dosage 20 mg, blood pressure falling, *D* six minutes later, total dosage 30 mg, pressure still falling, *E*, six minutes later, total dosage 35 mg, *F*, four minutes later, total dosage 45 mg, pulse barely perceptible, *G*, two minutes later total dosage 45 mg, respirations failing and *H* three minutes later, total dosage 55 mg, animal apparently dead

by Levine¹⁹ in studying the effects of digitalis bodies. Under light ether anesthesia, the femoral artery and vein were exposed and cannulated, 100 mg of heparin was injected intravenously to avoid coagulation, the arterial cannula was connected with a sensitive manometer and a glass buret containing mercuric chlorid in dilute solution in physiologic sodium chlorid solution was attached to the venous side. The customary galvanometric leads were established and, after a preliminary electrocardiogram, mercuric chlorid solution was run in intermittently, frequent tracings of the blood pressure and heart action currents being taken.

As may be seen in the accompanying figure, the smallest dose employed reduced the voltage, and slightly larger doses gave evidence of severe myocardial damage as shown by the abnormal ventricular complexes recorded, as well as by a coincident fall in peripheral blood pressure. Successive doses increased this effect, the blood pressure fell progressively, and the evidence of heart muscle damage proceeded. *F* and *G* are apparently the tracings of a dying heart, and death occurred with ventricular fibrillation. With slight variations, this evidence of toxic action of relatively small doses was present in other experiments. There is nothing specific about the later changes in the electrocardiograph, Gordon²⁰ obtains similar records in cats receiving quimidin intravenously, but they are not merely the accompaniment of death in the cat, as they do not appear when animals are bled to death. It was not intended to determine the toxic dose of mercuric chlorid by this method but to ascertain whether evidence of direct action on the heart from small quantities of drug, which might play a part in the intoxication, could be obtained. The quantities of mercuric chlorid per kilogram which showed this action were of the same order as might be assumed for absorbed mercuric chlorid from the average amount ingested by human beings.

Failure to demonstrate morbid changes at necropsy other than those of local escharotic action is not surprising. The degree of nephritis found in the second patient was considered fairly early for mercuric chlorid nephritis in man but Fiessinger²¹ examined the kidneys of guinea-pigs at intervals after intraperitoneal injection of from 0.008 to 0.017 gm of sublimate in solution, amounts that are of the same general magnitude per kilogram as the usual human dosage by mouth, and he described a patchy and irregular involvement of a few tubules after one hour of poisoning, in which the only lesions found were swelling of the cytoplasmic granules and slight pyknosis of the nuclei without exudate.

19 Levine, S. A. The Action of Strophanthin on the Living Cat's Heart, *J. Exper. Med.* **29** 485 (May) 1919.

20 Gordon, Burgess. Personal communication to the author.

21 Fiessinger, Noel. Note sur les Lésions Renales, au cours de l'Intoxication Mercurielle Massive, *Compt. rend. Soc. de biol.*, Feb. 16, 1907, p. 240.

or desquamation into the lumen. The changes found in this patient, however, could have had little to do with death. The rapidity with which nitrogen retention can develop is emphasized by Case 1, in which with anuria of less than fifteen hours, the level of nonprotein nitrogen reached 98 mg.

Of great interest were the high leukocyte counts (34,000 and 40,000) recorded in these fatal cases. In a number of other cases similarly high counts were observed only once. This was in a man, aged 25, whose blood showed 40,500 white cells per cubic millimeter eight hours after taking an unknown amount of mercuric chlorid, and who died fifty hours after the poisoning with a terminal Type IV pneumococcus pneumonia, showing at necropsy inflammation of most of the gastro-intestinal tract from mouth to colon, extreme necrosis of the renal tubules, pneumonia and fibrinous pleurisy. It is interesting that in this case, in spite of the development of secondary infection, after forty-eight hours the leukocytes numbered only 9,800. Heilborn²² found deep red marrow in the hollow bones of rabbits and the femurs of dogs experimentally mercurialized. Kaufmann²³ noted an increase in white blood cells and rapidly developing anemia in experimental poisoning. Clinically, Guillain and Gardin²⁴ saw a white count of 13,400 and anemia of 3,300,000 red cells on the third day in a case terminating in uremia on the eighteenth day. Vialard and Baril²⁵ counted 21,700 white cells with 89 per cent polymorphonuclear neutrophils on the thirteenth day after mercuric cyanid poisoning, and Outerbridge²⁶ found 14,400 leukocytes on the second day in a patient who recovered from vaginal absorption of mercuric chlorid after a stormy course. Weiss⁸ alone has apparently attached significance to this leukocytosis, which, he says, may reach 20,000 and then decline, or remain elevated and carry an unfavorable prognosis. Persistent elevation of the count we have not observed, but it would seem that early in the disease it is of definite importance as an index of the likelihood of recovery, as in ten other cases the degree of elevation of the white count corresponded closely with the severity of the poisoning, the patients with normal counts escaped colitis and

22 Heilborn, Max. Experimentelle Beiträge zur Wirkung subcutaner Sublimat-Injectionen, *Arch exper u Pharmacol* **8** 361 (Jan) 1878.

23 Kaufmann, Eduard. Die Sublimatintoxication, Thesis, Breslau, 1888, cited by Besseson, D. H. *Arch Dermat & Syph* **7** 332 (March) 1923.

24 Guillain, G., and Gardin, C. Physiologie Pathologique de l'Intoxication Mortelle par le Sublime, *Ann de med* **11** 338 (April) 1922.

25 Vialard and Baril. Etude sur deux cas d'Intoxication, dont l'un mortel par absorption d'un sel de mercure, *Bull et mem Soc med d hôp de Paris* **47** 907 (June) 1923.

26 Outerbridge, G. W. Complete Anuria Following a Mercuric Chlorid Douche, Recovery After Bilateral Renal Decapsulation, *J A M A* **80** 102 (Jan 13) 1923.

nephritis, and several with a moderate increase (up to 20,000) exhibited definite but mild signs and symptoms of one or the other.

Last, the recent revival of interest in chemical detoxication, stimulated by the work of McBride and Denmie,²⁷ leads to a word of warning. Early and intensive treatment with sodium thiosulphate may not prevent early toxic death, and the generally accepted scheme of therapy (for example, that of Lambert and Patterson¹⁰), forced fluids, alkali or its equivalent in alkaline tartrates and citrates, gastric lavage and colonic irrigations, should by no means be neglected. Attempts to prove experimentally the value of other antidotes²⁸ that seemed efficacious clinically have been fruitless, and Zeigler's comment that recovery apparently takes place independently of the administration or failure to administer any of these so-called specific chemical detoxicants seems well taken. Variations in the lethal dose by mouth are so extreme that a large number of clinical observations, with an equal number of controls, should precede conclusion as to the value of any single therapeutic measure in this disease.

SUMMARY

Death from mercuric chlorid taken by mouth may ensue within hours, apparently with circulatory collapse, with little renal damage and no evidence of uremia. Evidence is presented which suggests that direct myocardial damage may account in part, at least for this early toxic death. In three severely poisoned cases, the white count reached 34,000 or higher in a few hours, and it is suggested that the degree of elevation of the leukocytes may be an index of the severity of poisoning, with an unfavorable prognosis when levels of from 30,000 to 40,000 are found. Last, while it is not denied that sodium thiosulphate may have value in treatment, it should be emphasized that it may fail to exert detoxicant action, and should not be administered to the neglect of established therapeutic methods.

27 McBride, W. L., and Denmie, C. C. Treatment of Arsphenamin Dermatitis and Certain Other Metallic Poisonings, *Arch. Dermat. & Syph.* **7**: 63 (Jan.) 1923; Treatment of Arsphenamin Dermatitis, Mercurial Poisoning and Lead Intoxication. Further Observations, *J. A. M. A.* **83**: 2082 (Dec. 27) 1924.

28 Barbour, H. G. Mercuric Chlorid Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, *J. A. M. A.* **64**: 736 (Feb. 27) 1915. Zeigler, W. H. A Study of the Efficiency of Certain Antidotes in the Treatment of Acute Bichlorid of Mercury Poisoning, *J. Lab. & Clin. Med.* **10**: 59 (Jan.) 1925.

THE INORGANIC PHOSPHORUS AND CALCIUM OF THE BLOOD IN NEPHRITIS

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It has been recognized for several years that the terminal stages of nephritis are accompanied by an increase in the inorganic phosphorus of the blood serum and some decrease in the calcium

In 1915 Greenwald¹ reported observations on the acid-soluble (largely inorganic) and lipid phosphorus of human blood serum. He observed that normally the acid-soluble phosphorus as P varied between 2 and 6 mg per hundred cubic centimeters, but that in severe nephritis it might be considerably increased. A year later Marriott and Howland² confirmed these observations and pointed out that the retention of (acid) phosphate would seem to be sufficient to account for the degree of acidosis observed. They found further in most of their cases a marked reduction in the calcium of the serum. They state

What influence this low calcium content may have on the production of such symptoms as convulsions and hemorrhages can only be suggested. The low calcium content is referred to the excess of phosphates in the plasma. It has repeatedly been shown that phosphates administered in any form cause an increased elimination of calcium, chiefly by way of the intestine.

In 1917 Halverson, Mohler and Bergeim³ studied the serum calcium of several patients with severe nephritis and obtained figures as low as 7 mg. Denis and Minot⁴ in 1920 reported observations on the inorganic phosphorus of a comparatively large series of nephritic patients (eighty). They observed that the fatal cases showed a rapid and progressive increase in the plasma phosphate, figures more than ten times

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† Medical fellow of the National Research Council during part of this study

1 Greenwald, I. The Estimation of Lipoid and Acid-Soluble Phosphorus in Small Amounts of Serum, *J Biol Chem* **21** 29, 1915

2 Marriott, W M, and Howland, J. Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, *Arch Int Med* **18** 708 (Nov) 1916

3 Halverson, J O, Mohler, H K, and Bergeim O. The Calcium Content of the Serum in Certain Pathological Conditions, *J Biol Chem* **32** 171 (Nov) 1917

4 Denis, W, and Minot, A S. A Study of Phosphate Retention from the Standpoint of Blood Analysis, *Arch Int Med* **26** 99 (July) 1920

the maximal normal value being noted (over 40 mg in one case), the nonfatal cases, even though the patients were seriously ill, presented a relatively slight increase. As a result of these findings they suggested that the determination might possess considerable prognostic value. They found no concordance between the increased content of inorganic phosphate and the nonprotein nitrogen in confirmation of the findings of Greenwald, and Marriott and Howland. They also called attention to the lack of any definite relation between the plasma phosphate and the alkaline reserve, a finding of interest in connection with the suggested relation between the acidosis in nephritis and phosphate retention. More recently Denis and Hobson⁵ have determined the various inorganic constituents of the serum, both acids and bases, in a series of twenty nephritis cases. The series did not include the severe cases of the earlier paper, the inorganic phosphorus being as high as 10 mg in only one case. The lowest calcium observed was 7.6 mg. Feigl⁶ has likewise presented figures for the acid-soluble phosphorus, also the calcium, in a series of eight severe nephritic cases, the phosphorus varying between 7.2 and 14.5 mg per hundred cubic centimeters of serum and the calcium between 7.4 and 10.3 mg. Salvesen and Linder⁷ have recently studied the inorganic bases and phosphates in relation to the proteins of the blood in a series of fifteen cases of Bright's disease and heart disease. Their series included two cases of uremia, six cases of chronic glomerulonephritis and three cases of nephrosis. The two uremia cases showed calcium figures of 6.8 and 7.2 mg and inorganic phosphorus figures of 20.5 and 24.0 mg, respectively. They pointed out that the decrease in serum calcium in nonuremic cases of Bright's disease without phosphate retention paralleled the decrease in plasma protein. This they believed was due to a decrease in the nondiffusible portion of the calcium (20-45 per cent) which is bound to the plasma proteins. However, in the cases with phosphate retention they regard this as the probable cause of the reduction in the calcium, since Binger⁸ has shown that the injection of phosphates results in a lowering of the blood calcium.

5 Denis, W., and Hobson, S. A Study of the Inorganic Constituents of the Blood Serum in Nephritis, *J Biol Chem* **55** 183 (Feb) 1923

6 Feigl, J. Neue Beiträge zur Kenntnis der anorganischen Stoffe des Blutes, I, Kationen und Hyperphosphatämie bei Morbus Brightii, *Ztschr f physiol Chem* **3** 280, 1920

7 Salvesen, H. A., and Linder, G. C. Observations on the Inorganic Bases and Phosphates in Relation to the Protein of the Blood and Other Body Fluids in Bright's Disease and Heart Failure, *J Biol Chem* **58** 617 (Dec) 1923

8 Binger, C. Toxicity of Phosphates in Relation to Blood Phosphates and Tetany, *J Pharm & Exper Therap* **10** 105 (Aug) 1917

In two comparatively recent papers, de Wesselow⁹ has focused attention on the relation of the content of calcium, inorganic phosphorus and urea of the blood to the clinical symptoms and prognosis of nephritis, particularly when associated with uremia. He has presented some interesting data and raises a number of points, some of which will be discussed further in connection with our own data.

De Wesselow is of the opinion that although nitrogen retention is a valuable prognostic index of the severity of nephritis, nitrogen retention per se is harmless. He points out that on the average the retention of phosphates and urea runs a parallel course, and concludes that the excretory mechanism of the two bodies is therefore probably the same. He regards a marked increase of the inorganic blood phosphorus in nephritis as an extremely grave prognostic sign, and notes that the symptoms of uremia appear to show a close relationship to phosphate retention. The calcium content of the serum seemed to show an inverse relationship to the content of inorganic phosphorus. According to de Wesselow a diminished content of serum calcium is a bad omen, and appears to be connected with the generalized tremor and local twitchings of the final stages of uremia, but not to the generalized convulsions. Of ten fatal cases, in which the calcium was estimated, the serum contained less than 7 mg per hundred cubic centimeters in nine cases, the lowest observation being 5.1 mg.

OBJECTS OF PRESENT STUDY

Our interest in this general problem was aroused by the paper of Marriott and Howland in 1916 and we had compiled a considerable number of observations on the serum calcium prior to the present study, although the data¹⁰ were never reported in detail.

The present study was undertaken with the hope of securing added information on the following points: (1) the possible relation of a reduction in the serum calcium to the convulsions and muscular twitchings of terminal chronic interstitial nephritis, (2) the relation of the retention of inorganic phosphorus to the reduction in the serum calcium, (3) the relation of the rise in the inorganic phosphorus of the blood to the lowering of the plasma bicarbonate, and (4) a comparison of the rise of the inorganic phosphorus and creatinin as prognostic signs.

Observations were made on fifty-four patients, the majority of whom were suffering from chronic interstitial nephritis. The data are pre-

9 De Wesselow, O. L. V. On the Phosphorus and Calcium of the Blood in Renal Disease, *Quart. J. Med.* **16** 341 (July) 1923, The Immediate Prognosis in Nephritis, with Some Remarks on Uremia, *Lancet* **2** 163 (July 28) 1923.

10 Myers, V. C., and Killian, J. A. Chemical Changes in the Blood in Advanced Nephritis, *Proc. Soc. Biol. Chem.*, April, 1919, *J. Biol. Chem.* **41** 21, 1920.

TABLE 1—*The Inorganic Phosphorus and Calcium of the Blood in Nephritis*

Case	Age	Sex*	Date	Inorganic Phosphorus, Mg to 100 C c	Calcium, Mg to 100 C c	Urea Nitrogen, Mg to 100 C c	Creatinin, Mg to 100 C c	Uric Acid, Mg to 100 C c	Carbon Dioxid, per Cent by Volume	pH	Diagnosis and Remarks
1	26	♂	1/23/24	25.5	6.8	125	7.5		44		Chronic nephritis convulsions, received alkalali died 1/25
2	26	♂	8/ 8/23	20.2	9.5	98	19.6	6.8	20		Chronic nephritis, died
3	65	♂	5/ 5/24 5/ 8/24 5/12/24	18.2 11.1	6.9	167 165 142	18.7		31 33 36		Chronic nephritis diabetes, muscular twitchings 5/9, died 5/13
4	34	♂	5/28/24	17.4		147	27.4				Chronic nephritis, died 5/30
5	31	♂	9/ 5/23 9/10/23 9/15/23 9/17/23	12.6 15.6 16.4 17.2	5.6 4.8 3.8	197 106	22.7 25.0	9.3	20 37 56	7.37 7.35	Chronic nephritis, convulsions for ten minutes 9/9, died 9/17
6	8	♂	5/ 8/23 5/11/23 5/14/23 5/18/23 5/25/23 5/28/23 5/30/23 6/ 2/23	12.1 15.1 15.0 12.0 15.2 15.0 16.1	4.8 4.4 4.2 4.1	8.9 98 86 109	11.1 11.5 12.4	6.8	25 30 19 20 21 7.18 7.05	7.15	Nephrosis followed two years later by chronic nephritis, transfusion 5/25, convulsions 6/3, day of death
7	54	♂	3/26/24 3/28/24	12.1 14.4	7.8 6.9	108 139	21.0 21.1		27	7.23	Chronic nephritis uremia convulsions, died 3/29
8	15	♀	12/13/23 12/13/23	12.2 11.9	4.8	190	20.0	13.7	24		Chronic nephritis, convulsions one week before admission died (suffered from nephrosis in 1916)
9	46	♂	10/ 4/22 10/19/22 10/23/22 10/27/22 10/28/22 10/30/22 11/ 1/22	4.4 6.6 6.6 8.7 10.0 12.2 12.2	12.0 9.4 9.5 9.5	66 49 86 122 155	5.4 7.5 8.4 11.5 13.4	4.1 6.8 8.4	31 39 49		Chronic nephritis no convulsions, died
10	22	♂	4/24/23 4/30/23 5/ 7/23 5/14/23	9.2 10.8 10.4 11.9	5.5	130 112 122	20.5 23.0 20.3	29 7.8 7.7	7.16 7.22 43 40	7.28	Chronic nephritis convulsions 5/17, died 5/19
11	37	♂	6/ 4/23	11.9		111	10.2	4.6	20	7.17	Carcinoma of kidney convulsions 6/9 died
12	39	♀	11/26/23 11/28/23 12/ 3/23	11.8	8.2	56 75	7.5 9.3		55		Chronic nephritis no convulsions, died 12/4
13	30	♀	7/15/23	11.3		87					Chronic nephritis, died 7/15
14	50	♂	11/ 1/23 11/ 7/23	8.7 11.1		55 104	4.3 14.4	5.0 9.3	42 24		Chronic nephritis, died
15	41	♂	8/ 8/22	9.8	9.5	155	14.0		30		Chronic nephritis, died
16	46	♀	1/18/23 1/22/23 1/26/23 1/30/23 2/ 5/23 2/12/23 2/19/23 2/26/23 2/28/23	6.1 6.2 6.4 5.7 5.8 7.1 4.9 8.6 9.3	11.7 11.5 7.0	49 72 68 40 55 50 60 74	4.9 7.0 6.5 5.6 5.8 8.2 9.6	6.2 6.9 7.3 6.1 5.8 6.1 5.8 9.5	61 60 62 61 51 57 55		Chronic nephritis, uremia, hypertension mitral stenosis and insufficiency, convulsions 3/2/23, one lasting 2 minutes another 8 minutes died
17	65	♀	2/ 1/24 2/ 9/24	11.0 9.5	9.6 9.3	43 105	5.4 15.0	9.0	24	7.22	Chronic nephritis cardiac disease, bronchopneumonia 90 gm sodium bicarbonate given 2/8-9 died 2/10

* In this table ♂ indicates male ♀, female

TABLE 1—*The Inorganic Phosphorus and Calcium of the Blood in Nephritis—Continued*

Case	Age	Sex ⁺	Date	Inor- ganic Phos- phorus, Mg to 100 Cc	Cal- cium, Mg to 100 Cc	Urea Nitro- gen, Mg to 100 Cc	Creat- inin, Mg to 100 Cc	Uric Acid, Mg to 100 Cc	Carbon Dioxid, per Cent by Vol- ume	pH	Diagnosis and Remarks
18	19	♂	9/11/22 10/ 9/22	8.8 14.3	6.0	158	20.0	13.2	41		Chronic nephritis, died 10/10
19	38	♀	2/26/23 2/27/23 2/29/23 3/ 4/23 3/ 5/23 3/ 6/23 3/ 7/23 3/ 8/23	6.5 8.7 9.2	10.0 10.0	96 115 127 156 163 185 211 208	3.6 5.3 11.0	 12.0	52 58 43 56 58	7.47 7.48 7.48	Acute nephritis, acute mastoiditis, alkali given, died 3/9
20	32	♂	1/22/23 1/26/23 1/30/23	6.0 8.7 8.5		32 57 54	4.6 11.5 7.8	3.0 4.0 4.3	 33 38		Chronic nephritis, died
21	50	♂	3/ 9/24	8.0	5.4	172	11.5				Chronic nephritis, died 3/10
22	14	♂	7/21/24	7.7	7.9	59	8.6	5.0	42		Chronic nephritis, hypertension
23	46	♂	10/22/23 10/30/23 11/ 5/23	8.2 7.5	9.4 8.8	103 109 100	11.0 11.2 12.5		54 35 61	7.40 7.40	Chronic nephritis, no convulsions, discharged clinically improved 11/10
24		♂	6/ 1/23 6/ 2/23	7.5 7.3		82	7.2	4.9	 64		
25	37	♂	12/18/23	7.4	5.7	83	5.2		35		Chronic nephritis, discharged improved 12/24
26	13	♂	10/ 4/22 11/ 6/22 11/27/22 12/11/22 1/ 2/23 1/15/23 1/22/23 1/26/23 2/16/23 2/19/23 2/25/23	4.3 4.2 5.8 1.7 4.1 5.1 5.1 4.7 7.0 5.7 8.7	10.5 11.2 9.2 10.8 8.0 8.6 8.4	61 30 46 60 48 49 63 74 70	6.2 3.4 4.7 6.3 7.4 6.0 8.3 4.4 4.3	 4.7 5.0 5.3 5.6 7.6 7.5	42 54 63 51 56 61 51 52		Cardiorenal disease, no convulsions, died
27	36	♂	11/12/23	6.6	9.0	31	4.4	3.8			Nephrosis, chronic nephritis
28	33	♂	6/20/23 6/27/23 7/ 4/23 7/ 9/23 7/30/23 9/21/23	4.8 5.9 6.3 6.3 5.0 4.6	 8.6	47 70 34 63 24 22	3.7 5.0 2.8 3.4	3.8 4.8 3.6 4.4	 30 51 44	7.36	Cardiorenal disease, died 11/1
29	25	♂	4/17/23 4/27/23	6.1 7.0	7.7 6.6	60	9.0	5.3	31		Chronic nephritis discharged improved 4/25
30	26	♂	2/ 4/23 2/15/23	5.2 6.0	9.6 10.0	44 135	5.5 11.1		65		Chronic nephritis severe uremic convulsions, died 2/16
31	53	♀	1/19/23 1/22/23	5.2 5.9		24 24	3.4 4.1	3.5 3.6	38 33		Pyonephrosis, hypertension discharged clinically improved 1/22
32	44	♂	8/ 1/23	5.9		90	8.4				Chronic nephritis, died
33	65	♂	9/24/23 10/ 6/23 12/17/23	5.9 8.5 5.7	8.9 7.3	66 84 42	7.1 9.2 6.2	6.6	49 60		Chronic nephritis left hospital clinically improved 12/24
34	70	♂	10/13/22	5.7		63	5.0	4.2			Chronic nephritis
35	50	♂	3/ 9/23 3/12/23	5.7 6.3	7.6 8.3	74	7.9	5.7	29		Chronic nephritis, left hospital 3/20
36	50	♂	4/18/23 4/19/23 4/24/23	5.5 4.5 3.4	11.2 10.2 10.5	54 45 16	4.1 4.8	6.3 4.8 4.0	39 46 66	7.33 7.35	Prostatic hypertrophy operation, discharged improved 5/27

⁺ In this table, ♂ indicates male, ♀, female

TABLE 1—*The Inorganic Phosphorus and Calcium of the Blood in Nephritis—Continued*

Case	Age	Sex*	Date	Inor- ganic Phos- phorus, Mg to 100 O c	Cal- cium, Mg to 100 O c	Urea Nitro- gen, Mg to 100 O c	Creat- inin, Mg to 100 O c	Uric Acid, Mg to 100 O c	Carbon Dioxid, per Cent by Vol- ume	p _H	Diagnosis and Remarks
37	28	♂	1/17/24 2/ 5/24	4 7 5 5	8 7 8 9	13					Nephrosis, left hospital
38	38	♂	8/ 3/22	5 4		40	3 8	4 0	36		Chronic nephritis, died 9/5
39		♂	11/21/23	5 1		55	5 6	7 0	53		Chronic nephritis, died 11/21
40	64	♂	4/20/23	4 8		30	5 5	4 7			Prostatic hypertrophy, operation, discharged improved 5/27
41	65	♀	10/29/23 11/12/23 11/28/23 12/18/23 1/ 9/24	4 7 7 9 4 9 5 0 5 1	8 6 9 5	98 93 75 44 62	5 1 9 8 6 8 6 6 7 8	6 6 	64 43 34	7 36 7 38	Admitted 10/24 in coma due to cerebral arteriosclerosis, left hospital improved 1/16
42	53	♂	1/21/24	4 5	10 2	26	4 4		46		Cardionephritis
43	51	♂	6/21/23 6/27/23	4 4 3 6		38 26	3 1 4 4	4 3	54 45		Cardionephritis dis- charged improved 7/19
44	50	♂	1/22/23 1/30/23	4 1 4 2		28 33	4 2	5 1	56		Chronic myocarditis, arteriosclerosis, dis- charged improved 2/5
45	56	♂	6/11/23 7/ 2/23	4 0		45 32	3 1 4 5	 4 1	50 53		Prostatic hypertrophy operation, discharged improved 5/27
46	65	♂	10/30/22 11/ 6/22 11/21/22 12/ 4/22	3 4 3 4 3 3 3 8	11 5	28 25 29 29	3 8 3 0 3 9 4 0	5 7 4 5 3 8	 42 52		Cardionephritis, trans- ferred to Bellevue
47	63	♂	11/21/23	3 6		77	3 6		43		Prostatic hypertrophy, died 11/21
48	59	♂	1/30/23	3 6		17	3 8	2 9	55		Urethral stricture, died 2/5
49	24	♂	4/17/23 5/ 7/23	3 6	9 3	26 15	2 6	5 3	61		Mitral stenosis, cardiac decompensation, left improved 6/7
50	45	♂	1/22/23 1/30/23	3 5 3 0		43 21	4 1	4 0	42		Tumor of bladder, died 3/27
51	50	♂	8/ 6/24	3 4	10 6	43	5 5				Extreme cardiac decom- pensation
52	41	♂	11/21/22 11/28/22 12/ 5/22	3 0		40 64 21	3 6 5 6 3 0	4 2	48 60 53		Nephrectomy following ruptured kidney left improved 2/20/23
53	62	♂	10/25/22 10/30/22 11/10/22	2 3 2 4 2 3	10 0	51 25 13	5 1 3 3	4 5 5 4	34		Chronic mastoiditis, arterial hypertension, left improved 12/15
54	53	♂	1/30/23	2 3		17	3 5	3 4	62		Prostatitis, discharged improved 4/17

* In this table, ♂ indicates male, ♀, female

sented in Table 1. In addition to figures for calcium and inorganic phosphorus, observations are recorded for the urea nitrogen, creatinin, uric acid, carbon dioxide capacity (or content), and in some instances for the p_H . In most of the severe nephritis cases it was possible to follow the progress of the condition by serial blood analyses. The cases have been arranged in order of the magnitude of the inorganic phosphorus.

METHODS

Little need be said regarding the analytic methods employed, since they are described in detail by one of us ¹¹ elsewhere. However, as emphasis is being placed on the blood calcium and inorganic phosphorus the following comment may be made. The Briggs' modification of the Bell-Doisy method for inorganic phosphorus was used for the earlier determinations, but later the Benedict method was employed. With the Benedict method any hemolysis must be avoided, and for this reason serum was employed in the estimation of the inorganic phosphorus as well as for the calcium. The Clark method was used for the calcium, incorporating some of the suggestions of Tisdall for this determination.

COMMENT

The cause of the muscular twitchings and convulsions that occur in the terminal stages of chronic interstitial nephritis has been sought by various chemical researches during the last one hundred years. The term uremia doubtless originated from the observation made by Prevost and Dumas ¹² in 1821 that extirpation of the kidneys gives rise to a marked accumulation of urea in the blood. Simple urea retention, however, has not been seriously considered as the cause of so-called uremic convulsions for many years, although as pointed out by Hewlett, Gilbert and Wickett ¹³ the administration of large doses of urea sufficient to raise the blood urea to a comparatively high figure may give rise to definite symptoms. The two other nitrogenous waste products, uric acid and creatinin, appear to be quite as devoid of toxic properties. In the case of creatinin retention, the possible formation of methyl guanidin needs to be considered although there is as yet no definite evidence of such formation.

Can the muscular twitchings and convulsions of uremia be attributed to disturbances in the inorganic ions of the blood? Sodium and potassium are so constant in both normal and pathologic serums that they appear to be almost above suspicion in this connection. No special significance has been attached to the slight variations that occur in the magnesium. Since Binger ⁸ has shown that the injection of phosphates (acid, neutral or basic) into animals leads to a reduction in the blood calcium, this would seem to furnish the most plausible basis of explaining the lowering of the blood calcium in chronic interstitial nephritis. He has further pointed out that when basic and neutral phosphate salts are injected in quantity sufficient to lower the blood calcium tetany

11 Myers, V. C. *Practical Chemical Analysis of Blood*, St. Louis, 1924.

12 Prevost, J. L., and Dumas, J. A. *Examen du sang et de son action dans les divers phénomènes de la vie*, *Ann. de chim. et phys.* **23**, 90, 1823.

13 Hewlett, A. W., Gilbert, Q. O., and Wickett, A. D. *The Toxic Action of Urea in Normal Individuals*, *Arch. Int. Med.* **18**, 636 (Nov.) 1916.

results, but that tetany does not follow the injection of acid phosphate salts, despite the fact that the blood calcium is lowered by acid phosphate as well as by the basic or neutral salts. This doubtless explains why patients with chronic interstitial nephritis having blood calcium values below 7 mg per hundred cubic centimeters do not show symptoms of tetany, since all such patients suffer from severe acidosis¹⁴. In other words we have a condition comparable to that produced in animals by the injection of acid phosphate salts. That the tetany resulting from the injection of phosphates is due to the reduction in the blood calcium, and not directly to the phosphate administration, would seem apparent from the fact that the tetany of parathyroid deficiency is due to a lowered blood calcium. Here the tetany is relieved by calcium administration and furthermore the inorganic phosphorus of the blood is essentially normal.

TABLE 2—Cases Having Convulsions or Serum Calcium Figures Below 7 Mg or Both

Case	Inorganic Phosphorus, Mg	Calcium, Mg	Convulsions	Urea Nitrogen, Mg	Creatinin, Mg	Carbon Dioxid, Cc	Outcome
1	25.5	6.8	Yes	125	7.5	44	Died
2	20.2	9.5	None recorded	98	19.6	20	Died
3	18.2	6.9	Muscular twitchings	165	18.7	33	Died
4	17.4		None recorded	147	27.4		Died
5	16.4	3.8	Yes	106	25.0	37	Died
6	12.0	4.1	Yes	86	11.5	20	Died
7	14.4	6.9	Yes	139	21.0	27	Died
8	12.2	4.8	Yes	190	20.0	24	Died
9	12.2	6.5	No	155	13.4	35	Died
10	9.2	5.5	Yes	130	20.5	29	Died
11	11.9		Yes	111	10.2	20	Died
12	11.8	8.2	No	75	9.3	55	Died
16	5.8	7.0	Yes	40	6.5	62	Died
18	8.8	6.0	None recorded	158	20.0	41	Died
21	8.0	5.4	None recorded	1.2	11.5		Died
25	7.4	5.7	None recorded	83	5.2	35	Left hospital clinically improved
29	7.0	6.6	None recorded	60	9.0	31	Left hospital clinically improved

Our own data bearing on the possible relation of the blood calcium and phosphorus to the convulsive symptoms of terminal nephritis are summarized in Table 2. It will be noted that all of the first thirteen cases showing calcium values below 7 mg, with one exception, exhibited muscular twitchings, convulsions or both while Cases 2 and 12 with blood calcium figures of 9.5 and 8.2 mg, respectively, did not show such symptoms. Attention should be called to the fact that the four less severe cases at the end of Table 2 did not disclose symptoms worthy of note despite the comparatively low calcium values. These cases were

¹⁴ Chace, A. F., and Myers, V. C. Acidosis in Nephritis, J. A. M. A. 74:641 (March 6) 1920.

under observation for a comparatively short length of time however and it is quite possible that the symptoms in question may have been missed. A study of our own data leads us to conclude then that a relatively high percentage of cases of terminal chronic interstitial nephritis, exhibiting muscular twitchings or convulsions, have serum calcium values below 7 mg.

The comments of de Wesselow¹⁵ in this connection are of interest. He states

Apart from generalized convulsions, there are certain other nervous phenomena associated with uremia which may not improbably be related to the diminished content of the serum in calcium. These are the localized twitchings and general tremor which, though less striking symptoms than actual generalized convulsions, are certainly of worse prognostic import. In the material under discussion these symptoms were present in three patients, all of whom died. In all three the calcium of the serum had fallen to a lower figure than 7 mg per hundred cubic centimeters, and in the patient who showed these symptoms in the most marked form the calcium content was the lowest of the series (Case 9). It is noticeable that in such cases the calcium may fall to a level at which symptoms of tetany might be expected to appear. Actually no such symptoms are found, nor are Trousseau's or Chvostek's signs present.

Both Binger⁸ and Tisdall¹⁶ have clearly demonstrated that there is a marked reduction in the serum calcium following the intravenous injection of phosphates. After the intravenous injection of dibasic sodium phosphate in dogs Tisdall found (a) a reduction of the calcium from an average of 10.5 mg per hundred cubic centimeters to 6.2 mg, and (b) an increase of the inorganic phosphorus from about 5 mg per hundred cubic centimeters to an average of 19.0 mg. What is the relationship between the rise in inorganic phosphorus and the reduction of the serum calcium in the terminal stages of chronic interstitial nephritis? There is no uniform inverse relationship between the level of the inorganic phosphorus and the calcium in the different cases. This may be illustrated by Cases 1, 2, 5, 8, 12 and 15, for example. With inorganic phosphorus figures of 25.5, 16.4 and 12.2 mg, in Cases 1, 5 and 8, the calcium was 6.8, 3.8 and 4.8 mg, respectively, whereas in Cases 2, 12 and 15 with phosphorus figures of 20.2, 11.8 and 9.8 mg the calcium was 9.5, 8.2 and 9.5 mg respectively. However in the individual cases one may note a gradual fall in the calcium with the rise in the inorganic phosphorus.

As pointed out by Chace and Myers¹⁴ all patients with advanced chronic interstitial nephritis suffer from acidosis, and thus show low figures for the carbon dioxide capacity of the blood plasma. The most plausible explanation of the acidosis is that offered by Marriott and

15 De Wesselow (Footnote 9, first reference)

16 Tisdall, F. F. The Influence of the Sodium Ion in the Production of Tetany, *J. Biol. Chem.* **54**: 35 (Sept.) 1922

Howland,² namely, that the acidosis is due to impaired ability to excrete acid phosphate. How well then can the figures for the carbon dioxide capacity of the plasma be correlated with those for the inorganic phosphorus? The data recorded in Table 1 indicate that low figures for the plasma bicarbonate may be present in the absence of high figures for the inorganic phosphorus, but that cases showing high figures for the inorganic phosphorus are almost invariably accompanied by low figures for the carbon dioxide capacity of the plasma. In six of these patients (all the patients examined who did not receive alkali) the p_H of the blood plasma showed that the acidosis was definitely uncompensated.

TABLE 3—*Comparison of the Prognostic Value of Inorganic Phosphorus and Creatinin of the Blood in Nephritis*

Case	Inorganic Phosphorus, Mg to	Creat- inin, Mg to	Outcome	Case	Inorganic Phosphorus, Mg to	Creat- inin, Mg to	Outcome
	100 C c	100 C c			100 C c	100 C c	
1	25.5	7.5	Died	28	6.3	5.0	Died
2	20.2	19.6	Died	29	7.0	9.0	Clinically improved
3	18.2	18.7	Died	30	6.0	11.1	Died
4	17.4	27.4	Died	31	5.9	4.1	Clinically improved
5	17.2	25.0	Died	32	5.9	8.4	Died
6	15.2	12.4	Died	33	8.5	9.2	Clinically improved
7	14.4	21.0	Died	34	5.7	5.0	?
8	13.9	20.0	Died	35	6.3	7.9	Clinically improved
9	12.2	13.4	Died	36	5.5	4.8	Clinically improved
10	11.9	20.3	Died	37	5.5		Clinically improved
11	11.9	10.2	Died	38	5.4	3.8	Died
12	11.8	9.3	Died	39	5.1	5.6	Died
13	11.3		Died	40	4.8	4.7	Clinically improved
14	11.1	14.4	Died	41	7.9	9.8	Clinically improved
15	9.8	14.0	Died	42	4.5	4.4	?
16	9.3	9.6	Died	43	4.4	4.4	Clinically improved
17	11.0	15.0	Died	44	4.2	4.2	Clinically improved
18	14.3	20.0	Died	45	4.0	4.5	Clinically improved
19	9.2	11.0	Died	46	3.8	4.0	Left hospital
20	8.7	11.5	Died	47	3.6	3.6	Died
21	8.0	11.5	Died	48	3.6	3.8	Died
22	7.7	8.6	?	49	3.6	2.6	Left hospital
23	8.2	14.2	Clinically improved	50	3.5	4.1	Died
24	7.5	7.2	?	51	3.4	5.5	?
25	7.4	5.2	Clinically improved	52	3.0	5.6	Left hospital
26	8.7	8.3	Died	53	2.3	5.1	Left hospital
27	6.6	4.4	?	54	2.3	3.5	Left hospital

A number of the patients received sodium bicarbonate as may be noted in Table 1 under Remarks, or by the sudden rise in the figures for the carbon dioxide capacity. It has obviously been necessary to disregard these figures in formulating our conclusions regarding the relationship between reduction of the carbon dioxide capacity and the rise in the inorganic phosphorus.

Owing particularly to the question that has been raised as to the identity of the chromogenic substance formed in blood filtrates by picric acid and alkali, de Wesselow¹⁵ advocates the use of the inorganic phosphorus as a prognostic sign superior to the blood creatinin. In order to compare the blood creatinin with the inorganic phosphorus in the present series of cases, single determinations of these constituents

are retabulated for each of the cases in Table 3. In this particular table there appears to be little difference between the two determinations from a prognostic point of view. Unfortunately a number of the less severe cases were not followed after the patients left the hospital. There is little doubt about the reliability of inorganic phosphorus retention as a prognostic sign, but the creatinin is equally reliable and the retention appears to occur a little earlier than in the case of the phosphorus. Since the publication of our final paper¹⁷ on the prognostic value of the blood creatinin in nephritis in 1919, we have compiled observations on several hundred cases, and have yet to encounter a case at variance with our original conclusion, that in cases in which the creatinin rises above 5 mg per hundred cubic centimeters of blood the patients rarely show any marked improvement and almost invariably die within a comparatively limited time, the only exception being in cases in which the retention is due to some acute renal condition.

CONCLUSIONS

A relatively high percentage of cases of chronic interstitial nephritis with muscular twitchings or convulsions show values for the calcium of the blood serum below 7 mg per hundred cubic centimeters.

There is no uniform inverse relationship between the level of the inorganic phosphorus of the serum and the calcium in different cases. In other words the retention of phosphorus has a greater influence in some cases than in others. However, in individual cases one notes a gradual fall in the calcium with a rise in the inorganic phosphorus.

Low figures for the carbon dioxide capacity of the plasma may be present in the absence of high figures for the inorganic phosphorus, but cases showing high figures for the inorganic phosphorus are almost invariably accompanied by low figures for the carbon dioxide capacity of the plasma. Here the few observations recorded for the p_H indicate that the acidosis is generally of the uncompensated variety.

There is little doubt about the reliability of inorganic phosphorus retention as a prognostic sign in chronic nephritis, but the creatinin is equally reliable and the retention appears to occur a little earlier than in the case with the inorganic phosphorus.

¹⁷ Myers, V. C., and Kilham, J. A. The Prognostic Value of the Creatinin of the Blood in Nephritis, *Am J M Sc* **157** 674 (May) 1919.

ACUTE FEBRILE ANEMIA

A NEW DISEASE?

I C BRILL, M D

PORTLAND, ORE

At the present stage of medical progress one hesitates to present new clinical syndromes. However, the case here described presents a picture that, to my knowledge, does not correspond with any known clinical entity.

REPORT OF CASE

C E, an unmarried woman, aged 38, of good family and personal history, was seen by me for the first time May 7, 1925. The present illness was of two weeks' duration and began as an "attack of biliousness" characterized by vomiting, malaise and a feeling of weakness. The vomitus consisted of bile stained food and contained no blood. A few days later she developed nosebleed and severe pain in the occipital region. At this time her sister, who is a trained nurse, came to take care of her. She found the patient extremely ill, presenting a peculiar dark, glassy, "tobacco" color, with little brown spots in various parts of the body and a temperature of 101 F. Within the following day or two the patient sank very low, becoming listless and picking at the bed clothes. Her color gradually became pale and a generalized edema developed. There were several attacks of severe pain in the region of the spleen, these came on suddenly and lasted several hours each time.

A blood count, April 30, 1925, showed 27 per cent hemoglobin (Dare), 1,250,000 red cells, 5,750 white cells, with 61 per cent neutrophils, 36 per cent lymphocytes, 2 per cent eosinophils, and 1 per cent basophils. One week later, on the day of my first examination, the hemoglobin was so low that it was not possible to make an accurate reading, probably about 15 per cent. The erythrocytes numbered about 1,000,000, and the leukocytes about 5,000, with a differential count essentially the same as in the previous examination. Blood cultures taken three times at three day intervals were consistently sterile. The urine, on several examinations, showed a trace of albumin and a moderate number of pus cells. A stool examination revealed nothing of note. The gastric contents showed a total absence of free hydrochloric acid. Roentgen-ray examination of the lungs showed irregular shadows that were interpreted as patches of congestion or of bronchopneumonic consolidation.¹

The general condition of the patient seemed hopeless. There was a deathlike pallor, numerous petechial spots, and a glassy edema involving the entire body. There was no jaundice. The patient was in a stupor, with labored respiration of the sighing type. The tongue was swollen and ashy gray. The heart action was feeble, the lungs appeared to be flooded with edema. The liver and spleen appeared moderately enlarged to percussion, but neither organ could be felt under the ribs. The temperature varied between 100 and 101 F during most of the time, with an occasional rise to 103. The pupils were dilated and reacted sluggishly to light, the knee and ankle jerks could not be obtained.

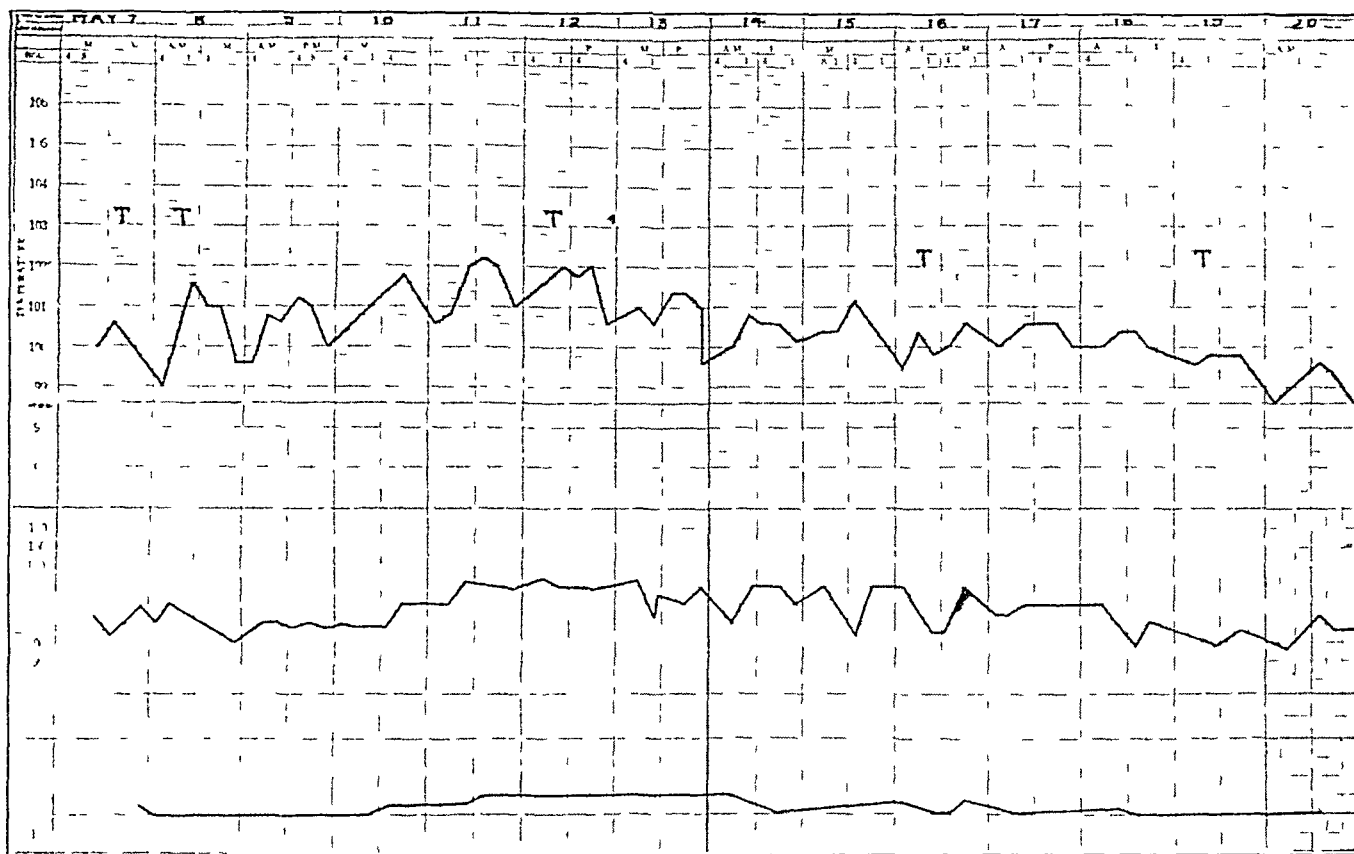
Shrinking from the idea of giving up without a fight, I suggested the use of blood transfusions, although I had no hope of recovery. A universal donor was secured and 300 cc of whole blood was transfused by the syringe method at the

* From the medical clinic of the University of Oregon Medical School

1 A more recent roentgenographic examination of the chest showed the lungs to be entirely clear.

patient's bedside. Surprising improvement in the patient's general condition followed. The procedure was then repeated and, in all, ten transfusions were performed between May 7 and June 12. The amount of blood given varied from 300 to 500 cc, and the intervals between transfusions varied from one day to one week. The patient showed a marked and steady improvement. The blood rose steadily, so that within a week after the last transfusion a practically normal count was obtained. By the end of June the patient was up and around enjoying normal health.

In addition to the transfusions the patient received daily ultraviolet (Alpine) radiations. At this time it cannot be definitely stated whether or not the radiations played any part in the patient's remarkable recovery.



Temperature, pulse and respiration curves in case reported. T, dates on which first five blood transfusions were given.

COMMENT

From the outset, it was evident that I was dealing with a hitherto undescribed disease. A careful search of the literature revealed only a single instance in which a case is reported resembling the one described here.²

The patient was a man, aged 26, admitted to the Prince Alfred Hospital, Sydney, Australia, Dec 17, 1901. His illness was of five weeks' duration and began with "sore throat and toothache." He apparently recovered from both these complaints in a few days, but continued to grow weaker, suffered from

² Macintosh, A. H., and Cleland, J. B. A Case of Rapidly Increasing Anemia with Irregular Pyrexia and Death, *Australasian M. Gaz.* 21:462 (Sept 20) 1902.

frontal headache, and rapidly became anemic. On examination he was found not emaciated, but pale and "lemon yellow." There was no jaundice. The blood examination on admission showed a hemoglobin of 26 per cent, red cells, 1,415,000, white cells, 14,000. The differential count is not reported, except for the statement that there were a large number of large leukocytes with neutrophil protoplasm granules. The shape of the red cells remained unaltered. The patient grew steadily weaker and twelve days after admission the blood examination showed red cells, 710,000, white cells, 20,000. The patient died the next day.

The postmortem examination revealed lesions usually seen in severe anemia including a "few small petechiae and vibices under the visceral pericardium" and a number of large bronchopneumonic patches in the lungs. Commenting on their case, the authors state: "This case, in its clinical and postmortem appearances, would seem to occupy a position midway between various forms of septicemia and pernicious anemia. It resembles the former in the raised temperature, in the bronchopneumonia, the petechiae and tendency to hemorrhages, the leukocytosis and the enlarged soft spleen, the latter, in the great diminution in the number of red cells, the clinical characteristics of a profound anemia, and the increased amount of iron in the liver."

While this article was being prepared for publication, I was agreeably surprised by Moschcowitz's³ illuminating report on his case of "an acute febrile pleiochromic anemia, with hyaline thrombosis of the terminal arterioles and capillaries." The resemblance between Moschcowitz's case, the case of Macintosh and Cleland, and the one here reported is indeed striking. It appears probable that the three cases represent the same morbid condition. If this is true, the three reports, together, constitute a fairly complete description of the clinical manifestations and pathologic anatomy of a hitherto unknown disease.

The essential features of this disease appear to be a more or less acute onset, a rapidly developing anemia resembling the pernicious variety of severity but retaining the characteristics of a secondary anemia with respect to the appearance of the blood corpuscles, and an irregular pyrexia, the temperature usually ranging between 100 and 102 F. The characteristic pathologic lesion, as described by Moschcowitz, is a plugging of the terminal arterioles or capillaries with hyaline thrombi. In a more advanced stage these hyaline masses are penetrated by fibroblasts and a "tubercle-like structure is formed."

Therapeutically, blood transfusions given in small amounts and at frequent intervals proved successful in one instance.

No light, however, is shed on the etiology of this strange disorder. The general clinical course is strongly suggestive of an infection, but blood cultures in two instances remained sterile. No mention is made of postmortem bacteriologic studies in Moschcowitz's case, except the statement that no bacteria were found in the tissues. Macintosh and

3 Moschcowitz, Eli. An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, *Arch Int Med* 36:89 (July) 1925.

Cleland obtained a growth of a "large bacillus with rounded ends and irregular staining" from the spleen examined fourteen hours after death. No blood cultures were made during life. It is hoped that the future may afford opportunity for the solution of this phase of the problem.

CHANGES IN RESPIRATION, IN CIRCULATION AND IN THE COAGULATION TIME OF BLOOD PRODUCED BY SODIUM CITRATE INJECTIONS

MINAS JOANNIDES, M D

CHICAGO

In a recent study of the toxicity of sodium citrate on exsanguinated dogs we noticed abnormal variations of the coagulation time of the blood¹ About this time Neuhof and Hirshfeld² published a paper asserting that intramuscular injections of sodium citrate in doses of 30 cc of 30 per cent solution for 150 pounds (68 Kg) would decrease the coagulation time of the blood So sure were these observers of their results that they advised the use of sodium citrate as a matter of routine in cases of actual or impending hemorrhage In view of the fact that sodium citrate ordinarily is regarded as an anticoagulant, a careful study of this phenomenon was attempted

It has been generally accepted that the citrate and oxalate group of anticoagulants affect the blood calcium so that it does not perform its essential share in the process of coagulation Oxalates are anticoagulants because they precipitate the blood calcium, thus rendering it inert in the presence of conditions that promote coagulation of the blood The action of sodium citrate is less clearly understood because of its complex formula Bloch³ and Mathews⁴ suggest that sodium citrate renders the blood calcium nonionizable (although in solution) and thus prevents its activity during coagulation That the blood calcium is affected by the sodium citrate is shown by the fact that if the proper amount of calcium were added to incoagulable citrated blood, it will coagulate promptly

It is beyond the scope of this article to discuss theories relating to the coagulation of the blood This has been done extensively by most workers on the coagulation of the blood The work of Hewson,⁵

1 Joannides, M, and Cameron, A L Citrated Blood Transfusions An Experimental Study of the Toxicity of Sodium Citrate in Exsanguinated Dogs, J A M A 82 1187-1189 (April 12) 1924

2 Neuhof, H, and Hirshfeld, S Intramuscular Administration of Sodium Citrate A New Method for the Control of Bleeding, Ann Surg 76 1 (July) 1922

3 Bloch, M A Study of the Autocoagulant Action of Sodium Citrate and the Part Played by Calcium in the Blood, Lancet 2 301 (Aug 7) 1920

4 Mathews, A P Physiological Chemistry, New York, William Wood & Co

5 Hewson, W The Works of William Hewson, London, Sydenham Society

Wooldridge,⁶ Morawitz,⁷ Howell,⁸ and Mills and Guest⁹ gives a fairly clear conception of the theoretical application of various findings in blood coagulation. Loucks,¹⁰ of the laboratory of physiology at the University of Minnesota, carried out an extensive series of experiments to determine the various factors involved in the coagulation of the blood. He found that calcium is absolutely necessary throughout the entire process of coagulation. It is necessary for the formation of thrombin. Calcium must be present for thrombin to act on fibrinogen. In other words, a calcium-free thrombin would not coagulate fibrinogen or blood. The work of Loucks disproves the theory of Mills and Guest⁹ that tissue fibrinogen unites with blood fibrinogen to form fibrin. They assert that in this process calcium acts as a connecting link. He found that calcium is necessary for the reaction to go on. Calcium was present in the final product but not as a chemical constituent of the fibrin molecule, because it could be easily washed out with water. It is possible that the so-called thrombin is a tissue fibrinogen complex, because Loucks found that calcium could be dialyzed neither from thrombin nor from tissue fibrinogen but that it could be removed by oxalic acid. This indicates that the calcium is in some way bound to the tissue fibrinogen and thrombin. Furthermore, he could not produce an active thrombin from calcium-free fibrin. The work of Loucks proves that calcium is absolutely necessary to all stages of blood coagulation and perhaps it acts only as a catalyst. On the basis of these facts, therefore, one would expect that sodium citrate would decrease the coagulability of the blood because, as Bloch³ suggests, it renders the blood calcium nonionizable and thus prevents either the first or second stage of coagulation.

TECHNIC

If one searches through the literature for an accurate method for determining the coagulation time of the blood, he will find descriptions of an innumerable number of methods. Hinman and Sladen¹¹ and,

6 Wooldridge, L. C. Croonian Lecture on the Coagulation of the Blood, in *On the Chemistry of the Blood, and Other Scientific Papers*, London, 1893, Further Observations on the Coagulation of the Blood, *J. Physiol.* **4** 226, 1882, The Coagulation Question, *J. Physiol.* **10** 329, 1889.

7 Morawitz. *Beitr. z. chem. Phys. u. Path.* **4** 381, 1903, *Deutsch. Arch. f. klin. Med.* **79** 1, 215, 1904, *Beitr. z. chem. Phys. u. Path.* **5** 133, 1904.

8 Howell, W. H. The Harvey Lectures, Philadelphia, 1916-1917, Series 12, p. 292, Prothrombin, *Am. J. Physiol.* **35** 474, 1914.

9 Mills, C. A., and Guest, G. M. The Role of Tissue Fibrinogen (Thrombokinase) in Fibrin Formation and Normal Clotting, *Am. J. Physiol.* **57** 395 (Oct.) 1921.

10 Loucks, M. M. Thesis for Master of Science Degree, Submitted to the University of Minnesota, 1925.

11 Hinman, F., and Sladen, F. J. Measurement of the Coagulation Time of the Blood and Its Application, *Bull. Johns Hopkins Hosp.* **33** 207, 1907.

later, Solis Cohen¹² give a complete review of the various methods used. In the majority of these methods the blood was removed either by puncturing the skin and squeezing out blood, thus bringing it in contact with the tissues, or by means of venipuncture. In the latter case the blood was manipulated considerably and a great portion of it came in contact with a foreign body, such as the surface of a small gage needle, during the process of removal. In view of the fact that we could cut down to the vein or artery of the dogs, we inserted short and fairly wide glass cannulas and allowed the blood to be received in our centrifuge tubes. We used graduated centrifuge tubes of uniform size and shape for our receptacles. These were cleaned with bichromate cleansing solution, then with distilled water, and finally with alcohol and ether before they were sterilized in the autoclave. A piece of cotton was inserted at the mouth of the tube just before the sterilization, and thus both moisture and dust were excluded from the tube. The blood was removed from the blood vessel by inserting a sterile, right angle, small glass cannula into the lumen of the exposed vessel. The cannulas were cleaned and dried in the same manner as the tubes. A new cannula was used for each determination. Care was taken not to allow the blood to come in contact with any tissues. In order to avoid the possibility of using stagnant blood, which perhaps may be undergoing changes of coagulation, we allowed a few cubic centimeters of blood to run out of the vessel and then took a series of samples. At least two tubes were used for each determination and the interval between these samples was only from five to ten seconds. We used from 2 to 5 cc of blood for each of our samples. After the cannula was removed the tissues were wiped clean and covered with sterile gauze. Care was taken not to allow any bubbles to get into the tubes. Those containing air bubbles were discarded. The tubes were kept in the palm of the hand and an attempt thus made to keep the blood as nearly as possible at body temperature. The tubes were tilted carefully and individually and thus the film on the surface was not broken. If the film was broken, the coagulation time was invariably prolonged. A series, five or more, of groups of normals was taken before the experimental procedure was begun. All our animals were kept under light ether anesthesia.

In our experiments the coagulation time was the time interval from the moment the blood left the vessel until a film appeared on the surface and was thick enough so that on inverting the tube the blood did not run out.

¹² Solis Cohen, Myer. The Coagulation Time of the Blood as Affected by Various Conditions, *Arch Int Med* 8 684 (Nov 1) 1911, 8 20 (Dec) 1911.

EXPERIMENTS AND RESULTS

In the first series of experiments we studied the effect of intramuscular injections of sodium citrate solution on the coagulation time of the blood. All the animals were kept under light ether anesthesia. No preliminary medication was given. Seven experiments were performed on dogs.

In one experiment 10 cc. of a 2 per cent solution of sodium citrate was injected into a dog weighing 55 pounds (24.9 Kg.). The trisodium citrate was used because, as Mellon¹³ and his co-workers described, the monosodium citrate and the disodium citrate are a possible source of toxic reactions because of their variations in the hydrogen ion concentration. In their experience the trisodium salt was the least toxic. Samples of blood were taken at ten minute intervals for one hour after the injections. The coagulation time before and after the experiment varied within the same limits. In the remaining six experiments a 30 per cent fresh solution of trisodium citrate was used. In three of these there was a slight and very transitory lengthening of the coagulation time of the blood, from about ten to fifteen minutes after the injection. In the remainder the coagulation time was within normal limits. Five experiments were performed on patients who had no apparent blood disease. In all but one, the coagulation time was much the same before and after the injection of 30 per cent sodium citrate solution into the gluteal muscles. In one patient the coagulation time dropped from nine minutes and forty-seven seconds to two minutes and thirty-five seconds, and was as low as five minutes and thirty seconds when determined six hours after the injection. Two samples were taken each time but not more than three determinations were made on each patient after the injection. The blood was drawn through a 20-gage needle into a syringe and then emptied into the sampling tube. Just what happened to cause a decrease in one and no change in the rest we cannot tell. The technic used in the patients was the same as that used by Neuhof and Hirschfeld,² with the exception of the use of procain for producing local anesthesia. This part was omitted because we did not desire to bring in any more sources of error than absolutely necessary. All the patients complained of severe pain at the site of injection. No toxic symptoms were noticed.

In another series of experiments the intravenous injection of trisodium citrate was studied. Various concentrations were injected. In one experiment five injections, 10 cc. each, of a 2 per cent solution of citrate, were made on a dog weighing 26 pounds (11.8 Kg.). No toxic effects were noticed, and the variations in the coagulation time were within the normal. Samples were taken from five to fifteen

13 Mellon, R. R., Hastings, W. S., and Casey, Gertrude. Observations on the Effect of Sodium Citrate on the Blood, *J. A. M. A.* **77** 1678 (Nov. 11) 1923.

minutes after each injection Sodium citrate was injected at fifteen minute intervals Our negative results made us consider the possibility of not injecting a sufficient amount of sodium citrate to cause any appreciable change in the coagulation time of the blood We tried, therefore, larger amounts and greater concentrations for our subsequent doses

Five experiments were performed with intravenous injections of a 10 per cent solution of citrate Two dogs died within a few minutes after the injection, while the other three passed through a period of respiratory and circulatory depression, and finally recovered spontaneously In all these animals the coagulation time did not change materially after the injection When greater concentrations were used, the amounts had to be diminished accordingly In three animals a 20 per cent solution of citrate was used One dog, weighing 145 pounds (66 Kg), after the injection of a 5 cc of a 20 per cent solution, almost instantly developed a general convulsion with marked opisthotonos and incontinence of urine The respiratory movements stopped The pulse was not palpable About forty seconds after the onset of these symptoms the dog took a few gasping breaths and the pulse could now be palpated It was 140 beats per minute One minute later there was a complete return to normal Samples of blood were not taken during the acute symptoms Two minutes and sixteen seconds after the injection the coagulation time was within normal limits At this time the animal was completely relaxed and breathed normally Ten minutes later, while the animal was apparently in good condition, an injection of 10 cc of a 20 per cent solution of citrate was given intravenously The respirations stopped instantly and permanently The heart beat was slowed down from 140 to 60 per minute The heart continued to beat for fourteen minutes and three seconds after the beginning of the last injection No coagulation time determinations were made at this time

In the second experiment two toxic doses of 5 cc of a 20 per cent solution were given to a dog weighing 34 pounds (15.4 Kg) The symptoms produced were those of circulatory and respiratory collapse with convulsions In this animal the symptoms persisted for 147 seconds When the dog was apparently normal again a third and fatal dose, consisting of 10 cc of 20 per cent sodium citrate, was given The blood assumed a peculiar purple and became incoagulable so that it could be siphoned out by attaching a cannula to the vessel and connecting the cannula to a tube leading down to a point below the level of the table Blood pressure and respiration determinations were made on this dog Physiologic sodium chlorid solution was used as the pressure fluid The systolic pressure dropped from 113 to 8 mm of mercury The respirations became so shallow that it was impossible to record them on the kymograph After the last injection.

the systolic pressure remained at the level of 8 mm of mercury for sixty seconds. It then suddenly rose to 160 mm of mercury, and after remaining close to that level for twenty-five seconds it gradually dropped to zero. In the third experiment a fatal dose of 10 cc of a 20 per cent solution of sodium citrate was given to a dog weighing 29.5 pounds (13.4 Kg). The usual toxic findings appeared, and were followed by death. At times there is a transitory stimulation of respiration preceding the depression. Our results correspond quite closely to those obtained by Salant and Kleitman,¹⁴ who found a fall in the arterial pressure. Similar results have been obtained by Love.¹⁵ He found that 50 mg of citrate per kilogram given intravenously to small or medium sized dogs caused a depression of the heart and of the blood pressure. The blood pressure rose to normal or a few millimeters above normal at the end of a minute. Larger doses caused a sharper final rise of the blood pressure.

Much the same results have been obtained in a series of fourteen experiments in which intravenous injections of 30 per cent citrate solution were made. Realizing that there must be a definite association between the changes in coagulation and the acute toxic symptoms, we attempted to determine the coagulation time of the blood at the height of the toxic manifestations. Blood taken during this time was found to remain incoagulable for forty-eight hours after the injection. On the other hand, as the symptoms subsided the samples would show variations close to normal coagulation time. We assumed, therefore, that something happens to the blood or tissue calcium to cause convulsions and changes in the coagulation of the blood. Calcium chlorid was used, therefore, to counteract the effect of citrate. In one case 20 cc of 30 per cent calcium chlorid was injected thirty seconds after the injection of 10 cc of 30 per cent sodium citrate. There was an immediate and complete relaxation of the animal without any more convulsions. The respirations now became deeper and regular. During the acute symptoms samples of blood showed no coagulation for forty-eight hours. On the other hand, immediately after the injection of calcium and the subsiding of toxic symptoms the blood coagulated within the normal limits. The unusual effect of the calcium injection was that the animal, which weighed only 31 pounds (14.1 Kg), received a total of 66 cc of 30 per cent solution, or 19.8 Gm of sodium citrate, and did not die.

In view of the fact that very acute symptoms developed with great concentrations of the citrate, we attempted to study the cumulative

14 Salant, W., and Kleitman, N. Studies on the Pharmacology of Sodium Citrate. I, The Influence of Sodium Citrate on Respiration and Circulation, *J Pharm & Exper Therap* **20** 481 (Jan) 1923

15 Love, G. R. Studies on the Pharmacology of Sodium Citrate on the Circulation, *J Lab & Clin Med* **9** 175 (Dec) 1923

effect of citrate injections on the coagulation time A 2 per cent solution was used and was injected intravenously from a buret at a constant rate The animal that weighed 17 pounds (7.7 Kg) was apparently normal until 200 cc of the solution was injected From then on the respirations became shallower and slower till they stopped, when 300 cc was injected When 280 cc of citrate was injected samples of blood did not coagulate for forty-eight hours They were kept at room temperature and discarded after forty-eight hours This experiment shows quite emphatically that both the amount of sodium citrate and the concentration of the solution must be carefully considered

Seven experiments were performed to determine the effect of intravenous injections of 0.2 per cent sodium citrate solution injected in combination with 0.75 per cent sodium chlorid solution In all these experiments there was a definite but transitory decrease in the coagulation time of the blood The coagulation time returned to normal within an hour The greatest coagulability was noticed within from three to five minutes after the injection of quantities of from 250 to 400 cc of the combined solution When sodium chlorid alone was injected we found no deviation from the normal

Small, repeated hemorrhages, produced, for instance, by taking several samples of blood, had no appreciable change on the coagulation time of the blood Sudden hemorrhages in which amounts of from 250 to 300 cc of blood were removed showed a definite decrease in the coagulation time of the blood This decrease in time became even more pronounced when the blood was reinjected as a 0.2 per cent citrated blood solution The return to normal was prompt in all cases Four such experiments were performed with uniform results

Samples of blood were taken from the artery and from the vein to determine possible differences in the coagulation time of the blood In two such experiments there was no appreciable difference between the two sources

Salant and Wise¹⁶ made careful determinations of the fate of sodium citrate in the blood and in the urine By using a modification of Deniges' test they found that sodium citrate disappears rapidly from the circulation after intravenous injections into dogs and into cats No sodium citrate is found in the urine when doses under 0.5 Gm per kilogram are given intravenously Sodium citrate was evidently eliminated rapidly in our dogs because the animals recovered quite promptly We had a similar experience in the case of a patient who had gangrene of his toes secondary to polycythemia vera On the basis of Willy Meyer's¹⁷ report, the house officer injected large doses of

16 Salant, W., and Wise, L. E. The Action of Sodium Citrate and Its Decomposition in the Body, *J Biol Chem* **28** 27 (Dec) 1916

17 Meyer, Willy The Conservative Treatment of Gangrene of the Extremities Due to Thrombo-angitis Obliterans, *Ann Surg* **63** 280 (March) 1915

sodium citrate intravenously Willy Meyer reported satisfactory results when this salt was used in connection with systematic infusion of Ringer's solution This patient received nine intravenous injections of a 3 per cent watery solution of sodium citrate The amounts used varied from 300 to 450 cc of a 3 per cent solution Studies on the coagulation time showed no appreciable change from the normal This patient weighed 147 pounds (66.7 Kg) We were present during one of these injections We noticed that when he received about 200 cc of the solution he volunteered the statement that he felt "funny" By this he meant that he had dimness of vision and a sense of constriction in his head For a few moments he was apparently unconscious because he did not respond to questions nor did he know of the questions when asked about them at a later time At the beginning of the injection the pulse rate was 120 beats per minute During the acute symptoms it became only 80 per minute As soon as the injection was stopped the symptoms disappeared very promptly Unfortunately, the injections of sodium citrate did not improve the gangrene We agree with Chemisse¹⁸ who warns against the indiscriminate use of sodium citrate This drug is dangerous when used in large doses but useful in smaller doses, such as those used for transfusion purposes Fortunately, it is eliminated very promptly, so that even with large doses the patient may have a chance to recover spontaneously

SUMMARY AND CONCLUSIONS

1 Our studies on man and on the dog show that the injections of sodium citrate do not usually increase the coagulability of the blood

2 Intramuscular injections are less dangerous than intravenous injections

3 A 3 per cent solution of sodium citrate, which is isotonic with blood, has been fairly well tolerated by a patient who received from 300 to 450 cc intravenously This practice, however, should be discouraged

4 Intravenous injections of great concentrations of sodium citrate are dangerous because they cause immediate respiratory and circulatory collapse

5 Calcium chlorid given promptly during the height of toxic symptoms may save the animal from death But calcium chlorid itself is a dangerous drug if injected intravenously in large doses

6 The toxic symptoms must in some way be associated with changes that concern the coagulation of the blood, because the latter becomes incoagulable under these conditions As soon as the toxic symptoms subside the coagulation time of the blood becomes normal

18 Chemisse, L. Le Citrate de soude dans le traitement des affections vasculaires, *Presse med* 30 258 (March 25) 1922

7 Shallow, slow breathing, a rapid and later slow pulse rate, convulsions, at times salivation and incontinence of urine, with a drop in the systolic pressure and increased coagulation time, mark the presence of toxic effects of sodium citrate

8 Small, repeated hemorrhages apparently have no effect on the coagulation time. On the other hand, when larger amounts of blood are removed they cause an increased coagulability of the blood. Citrated blood transfusion under such conditions increases the coagulability of the blood still more.

9 There is no apparent difference in the coagulation time of the arterial and of the venous blood.

10 Injections of 0.2 per cent sodium citrate solution in a 0.75 per cent sodium chloride solution invariably decrease the coagulation time of the blood and cause no toxic symptoms if the citrate dose is within the subtoxic limits.

11 Sodium citrate apparently disappears from the blood stream promptly since the toxic symptoms produced by the salt disappear quite promptly.

12 Sodium citrate used in amounts corresponding to those for blood transfusion is a useful drug. In larger amounts or concentrations it is a dangerous drug.

TESTING OF LIVER FUNCTION

I DETOXICATION BY THE LIVER [†]

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AND

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NEW YORK

The liver, our largest gland, has numerous and varied functions, and hence a most complex physiology. It plays an important rôle in the metabolism of carbohydrates, proteins and fats, it forms bile salts and helps form and excrete bile pigments, it modifies various substances produced in the body in such a way as to make these substances more easily handled and less harmful to the body, it performs detoxication work.

An exact determination of the condition of the liver in any normal or pathologic case would, of course, presuppose a complete understanding of its performance of all these functions. But since this is quite impracticable, one would rather attempt the study of merely one or two functions, which while sufficiently easy of determination, and this by a test not too cumbersome for manipulation, would yet give a fairly good estimate of the general functional condition of the organ. Several such tests have been tried but none has proved completely satisfactory. We shall attempt to add another contender to these liver function tests.

A study of the chemical defense mechanism of the animal body has shown that although in general definite processes of detoxication are by no means specific for the various animals, yet certain chemical and metabolic reactions may at times be limited to a single species. One of the best known differentiations of this kind is the detoxication of benzoic acid in the avian body by ornithine,¹ while in the other animals the amino-acid glycocoll² is employed. A still more interesting case, as shown by one of us, is the use of another amino-acid, glutamine (by the human being only), in the detoxication of an acid produced during intestinal putrefaction.³ In this one reaction at least the process occurring in the human body is entirely different from the method in which this same putrefaction product is handled by the lower animals.

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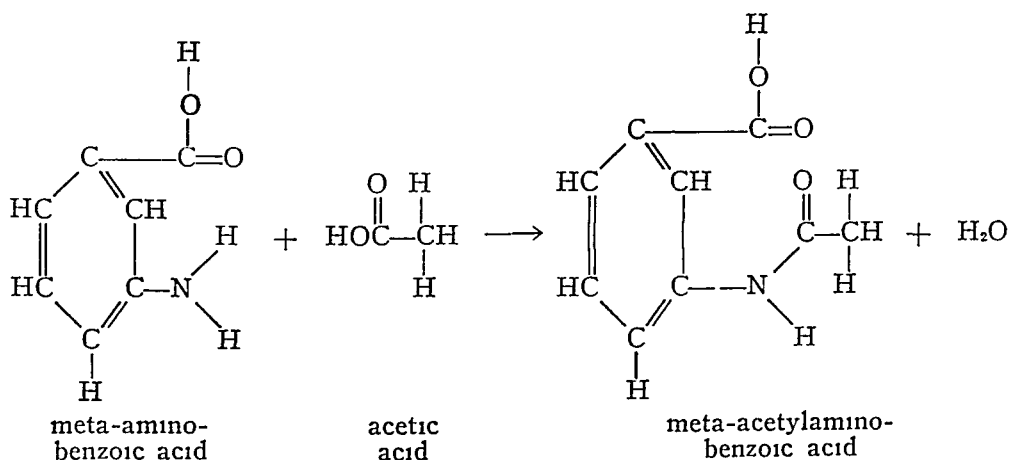
1 Jaffe, M. *Ber d deutsch chem Gesellsch* **10** 1925, 1877.

2 Woehler, F. *Ztschr f physiol Chem* **1** 125, 1824.

3 Thierfelder, H., and Sherwin, C. P. *Ber d deutsch chem Gesellsch* **47** 2630, 1914.

It has been pointed out in a previous article⁴ that the defense against foreign organic molecules is maintained by the use of seven or eight general reactions. We were surprised some time ago to find that acetic acid when used by the animal body as a defense against amino compounds is not limited to one or two aliphatic compounds and to the side chain amino groups of two or three aromatic substances, but is employed by the normal human body⁵ in the detoxication of certain aniline derivatives in which the amino group is firmly bound to the benzene ring.

Salkowski⁶ described the feeding of meta-aminobenzoic acid to a dog, after which he recovered from the urine two compounds that he believed to be uraminobenzoic acid and aminohippuric acid, the former a union of the meta-aminobenzoic acid through its amino group with urea, and the latter a combination through the carboxyl or acid group with glycocholl. While these reactions in vivo seemed most logical, the yields of the compounds isolated by him were most unsatisfactory and the analyses also were none too convincing. A number of years later it was found by Cerecedo and Sherwin⁷ that para-aminophenylacetic acid, the homolog of Salkowski's compound, when fed in varying doses, was always detoxicated by the dog through a union with glycocholl, while by the human being and rabbit it was excreted as a combination with acetic



acid. As Salkowski had described but a single reaction in the case of human beings, dogs and rabbits, it was decided to repeat the work on meta-aminobenzoic acid. Subsequent work by Muenzen, Cerecedo and one of us⁸ showed that meta-aminobenzoic acid when fed to a dog was

4 Sherwin, C. P. *Physiol. Rev.* **2**, 238 (April) 1922.

5 Muenzen, J. B., Cerecedo, L. R., and Sherwin, C. P. *Proc. Am. Soc. Biol. Chem.* **19**, 16, 1925.

6 Salkowski, E. *Ztschr. f. physiol. Chem.* **7**, 93, 1882.

7 Cerecedo, L. R., and Sherwin, C. P. *J. Biol. Chem.* **62**, 217 (Nov.) 1924.

8 Muenzen, J. B., Cerecedo, L. R., and Sherwin, C. P. Unpublished data.

largely excreted unchanged, only traces of a glycocholic compound (meta-aminohippuric acid) being found. When the meta-aminobenzoic acid was fed to human beings and rabbits, however, there always appeared a considerable quantity of meta-acetylaminobenzoic acid, that is, a combination of meta-aminobenzoic acid with acetic acid. The acetic acid was supplied by the organism and was coupled with the amino group of the amino-acid with the splitting out of a molecule of water. The reaction is pictured on the preceding page.

After obtaining such results with the meta compound, both the ortho-aminobenzoic acid (anthranilic acid) and the para-aminobenzoic acid were fed to human beings, dogs and rabbits. It was found that the anthranilic acid while quite toxic was not acetylated (i.e., joined with acetic acid) but was excreted unchanged by both the human being and the rabbit. On the contrary, the para-aminobenzoic acid not only proved to be so nontoxic that as much as 5 Gm. could be taken by a human being without causing discomfort, but in addition it was much more completely acetylated by both the human being and the rabbit than the meta-aminobenzoic acid described above.

Certain of these detoxication reactions have at different times been used as organic function tests, one of the best known cases being the hippuric acid synthesis employed by Kingsbury as a renal function test.⁹

Since Knoop and Kertess¹⁰ have shown that the acetylation of phenylaminobutyric acid is brought about by the perfused liver, we thought it worth while to study the acetylation of aminobenzoic acid in the normal human body and compare these results with those obtained after feeding the same compound to persons with some known "liver derangements." For this work we chose the para-aminobenzoic acid as it was both relatively inexpensive and at the same time less toxic than the meta-aminobenzoic acid. Moreover, it seemed to combine in the human body with acetic acid in much larger proportions than the meta compound.

METHOD

The method thus far employed is too cumbersome to be used as a clinical method even should the test prove otherwise satisfactory. We are at present trying to devise a simpler means.

The twenty-four hour urine volume is collected after feeding the subject 5 Gm. of para-aminobenzoic acid and is thoroughly mixed. Then 100 cc. is measured out, exactly neutralized to litmus with an alkali and evaporated to a thick syrup over a water bath. The neutralization prevents the escape of all volatile acids on evaporation. The syrupy residue is cooled, made acid with sulphuric acid to Congo red indicator,

⁹ Kingsbury, F. B., and Swanson, W. W. *J. Biol. Chem.* **46** 4, 1921.

¹⁰ Knoop, F., and Kertess, E. *Ztschr. f. physiol. Chem.* **71** 252, 1911.

then extracted with ether (preferably in a rotary type extractor) for six hours. As a rule an hour and a half is sufficient to extract all the acetylaminobenzoic acid. This ether extract contains all the acetylaminobenzoic acid, but there is also present with it the uncombined para-aminobenzoic acid to a large extent.

The ether is quickly removed by evaporation or distillation, and the residue, containing the free and acetylated aminobenzoic acid, is then taken up with 100 cc of 20 per cent sulphuric acid, placed in a distilling apparatus and boiled for half an hour. Into the distilling flask is inserted a dropping funnel through which water is allowed to drop into the distilling flask as fast as it distils out, in this way the contents of the flask are kept equivalent to a 20 per cent solution of sulphuric acid. The distillate is received in a flask containing tenth normal sodium hydroxid. The sulphuric acid coming in contact with the free para-aminobenzoic acid forms the addative sulphate compound which, being soluble and nonvolatile, remains dissolved in the flask and does not distil over. Cold sulphuric acid has no effect on the acetylated aminobenzoic acid but boiling hydrolyzes the compound into acetic acid and para-aminobenzoic acid, the former distilling over while the latter is held in the flask as a sulphuric acid complex.

After the distillation is complete the tenth normal sodium hydroxid solution, into which the acetic acid distillate was received, is titrated with tenth normal acid solution. From the difference in the number of cubic centimeters of tenth normal alkali originally taken and of tenth normal acid required for the back titration the amount of acetic acid in the distillate can be calculated and, consequently, the amount of para-aminobenzoic acid acetylated after the 5 Gm dose can be determined.

In order to determine the normal acetylation value for a given dose of para-aminobenzoic acid we administered to each of ten normal subjects 5 Gm of para-aminobenzoic acid. The urine was collected in two portions, the first portion starting immediately after the ingestion of the substance and ending with the expiration of the first twenty-four hours, and the second portion beginning with the twenty-fifth hour and ending with the forty-ninth hour. These samples were treated as follows. One-half the sample was evaporated to a thick syrup and repeatedly extracted with ethyl acetate. The resulting acetylaminobenzoic acid was then recrystallized from hot water and weighed as pure para-acetylaminobenzoic acid. The other half of the sample was worked up according to the clinical method (described above), that is, by determining (in triplicate) the amount of acetic acid formed by hydrolysis of the acetylated aminobenzoic acid.

The acetic acid method (clinical method) gives results that are always somewhat higher than those obtained by the extraction method. Thus,

according to Table 1, the average amount of benzoic acid acetylated during the first twenty-four hours as determined by the extraction method is 66.5 per cent, while according to the clinical method it is 68.5 per cent. The amount detoxicated during the second twenty-four hours is quite variable according to the extraction method, while the quantities present are too small to be determined accurately by the clinical method. This difference between the results of the two methods can be accounted for in two ways. First, there is always a slight loss in extracting and recrystallizing the para-acetylamino benzoic acid. Second, there is always a small amount of hippuric acid present in a twenty-four hour sample of urine which on hydrolysis with a mineral acid breaks up into glycocholic and benzoic acid. The latter, being volatile, thus augments the total acidity in the distillate and is counted as acetic acid.

In the clinical work the average amount of a 5 Gm. dose of para-aminobenzoic acid acetylated during the first twenty-four hours by a normal human being, namely, 68.5 per cent as determined by the clinical method, was taken as 100 per cent efficiency. Thus, for example, if in a pathologic case 50 per cent is acetylated instead of the normal amount of 68 per cent, then $50/68 = 73.5$ per cent, that is, the efficiency as measured by the ability to detoxicate para-aminobenzoic acid by acetylation is 73.5 per cent normal.

Through the courtesy of Dr. Lewis K. Neft, the test was applied to patients in the medical wards of the Harlem Hospital. The cases chosen were those that exhibited probable liver damage and included carcinoma of the liver, cholecystitis, cirrhosis hepatitis (toxic) due to arsphenamine, catarrhal jaundice, abscess of the liver, and carcinoma of the head of the pancreas. Four patients were operated on and in two others necropsy was performed. In several, the phenoltetrachlorophthalin liver function test of Rosenthal was used, and also icteric indexes measured with the 1:10,000 potassium dichromate standard. The technic of administering the para-aminobenzoic acid together with the method of carrying out the test was the same as that described in the discussion of the normal cases. The results are given in Tables 1 and 2.

COMMENT AND SUMMARY

In this short series of cases the degree of liver function efficiency as determined by the acetylation of para-aminobenzoic acid coincided with the approximate estimation of the same as judged from the clinical picture. In Cases 1 and 4, Table 1, in which no acetylation had taken place, necropsy revealed a most extensive involvement of the liver by carcinoma. Patient 10, Table 1, had a moderately large solitary liver abscess which was sterile and which failed to show amebas on repeated

warm stage examination This patient had a 60 per cent test, was operated on and had an uneventful recovery Patient 9, Table 1, was suffering from a severe grade of chronic nephritis and at the time of the test was in a preuremic state Nevertheless this patient was able to

TABLE 1—*Pathologic Subjects*

Sub ject	Date	Weight, Pounds	Age	Diagnosis	Normal* Acetylation, per Cent	Remarks
1	6/ 6/24	110 (49 9 kg)	58	Metastatic carcinoma of liver	0	Necropsy extensive carcinoma of liver
2	6/ 5/24	150 (68 kg)	59	Cirrhosis of liver	40	Discharged at own request
3	5/15/24	160 (72 6 kg)	53	Cholecystitis	70	Operation chronic cholecystitis
4	8/22/24	100 (45 4 kg)	48	Carcinoma of liver	0	Operation extensive carcinoma of liver
5	9/20/24	187 (84 8 kg)	56	Carcinoma of head of pancreas	75	Phenoltetrachlorphthalein test 25 per cent in 1 hour, icterus index 125
6	9/20/24	160 (72 6 kg)	26	Cholecystitis	86	Operation negative findings, complete recovery
7	10/ 1/24	130 (59 kg)	69	Catarrhal jaundice	83	Phenoltetrachlorphthalein test 3 per cent in 1 hour, complete recovery clinically
8	9/26/24	118 (53 5 kg)	49	Cerebrospinal syphilis with possible arsphen- amine intoxication	84	Faint icterus, cleared up rapidly
9	11/17/24	110 (49 9 kg)	62	Chronic nephritis	93	Preuremia, marked retention of blood metabolites, died 6 days after test
10	1/ 8/25	130 (59 kg)	29	Abscess	60	Operation followed by recovery
11	6/ 9/25	155 (70 3 kg)	62	Cardiac renal disease	91	Cardiac decompensation with general anasarca

* By normal acetylation (i e., 100 per cent) is meant the 68.5 per cent of ingested acid acetylated by a normal subject

TABLE 2—*Normal Subjects*

Sub- ject	Sex*	Age, Years	Weight,		Acetylamino benzoic Acid Isolated		Acetylated		Acetylated According to Clinical Method	
			Pounds	Kg	First 24 Hour Urine, Gm	Second 24 Hour Urine, Gm	First 24 Hours, per Cent	Second 24 Hours, per Cent	Per Cent	Average
1	♂	38	137	62.1	4.29	1.21	64	18	66, 66, 68	67
2	♂	21	147	66.7	4.18	1.01	64	15	69, 67, 68	68
3	♂	19	129	58.5	4.55	0.0	69		70, 69, 71	70
4	♂	29	132	59.9	4.40	0.39	67	6	69, 69, 64	67
5	♂	20	140	63.5	4.66	0.97	71	15	70, 71, 71	71
6	♂	32	178	80.7	4.22	0.13	64	2	67, 69, 70	69
7	♂	22	156	70.8	4.41	1.12	67	17	71, 68, 68	69
8	♂	23	112	50.8	4.48	0.67	68	10	70, 70, 71	70
9	♂	21	142	64.4	4.40	0.18	67	3	72, 68, 67	68
10	♂	19	137	62.1	4.16	0.74	64	11	67, 65, 65	66

Each subject ingested 5 Gm. of para aminobenzoic acid as a solution of the sodium salt

* In this column, ♂ indicates male, ♀, female

acetylate between 90 and 93 per cent of the normal amount She died only six days later This would seem to indicate that severe nephritis does not interfere with the estimation of liver function by this test Patient 11, Table 1, had chronic nephritis with marked cardiac changes and cardiac decomposition, showing general anasarca, large liver and ascites This

patient also returned a practically normal reading (91 per cent) Here we were dealing with the enlarged liver of chronic passive congestion in which condition the liver apparently functions well This has been our result with the dye test also The case of cirrhosis, in giving a 40 per cent normal acetylation value, indicated moderately severe damage to the liver Catarrhal jaundice and chronic mild cholecystitis gave results only slightly short of normal These cases were quite mild from clinical signs, symptoms and the lack of intoxication

These results indicate in general that severe liver damage gives low readings (zero with the two carcinoma cases), that mild liver involvement (clinically) gives only slightly lowered readings, as in Cases 3, 6 and 7, while diseases of other organs though severe do not give lowered readings, as in Cases 9 and 11

The threshold at which a subnormal reading first occurs, or the amount of liver tissue which has to be destroyed before changes in the test take place, is being studied at present

Though the paucity of cases in this preliminary paper does not warrant the drawing of any sweeping conclusions regarding the ability and the accuracy of this test for measuring liver function impairment, and still less for detecting small deficiencies, however we may safely say

- 1 The acetylation of para-aminobenzoic acid takes place in the liver (Neuberg)
- 2 The reaction offers an index of liver function
- 3 The test is probably not interfered with by severe cardiac or renal diseases
- 4 Clinically the test is easily performed
- 5 At present, however, the quantitative chemical estimation of the acetylated para-aminobenzoic acid in the urine is cumbersome

PAROXYSMAL DYSPNEA AS A SYMPTOM OF SYPHILITIC AORTITIS^{*}

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AND

WILLIAM H RESNIK, M D

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Paroxysmal dyspnea is so common a manifestation of aortic insufficiency dependent on syphilitic aortitis, often, indeed, being the first symptom of this disease, that it has been generally accepted that it is due directly to the presence of syphilitic aortitis, particularly when the lesion is situated at the root of the aorta¹ This view is apparently strengthened by the fact that paroxysmal dyspnea is practically never associated with aortic insufficiency of rheumatic origin² Our own experience in this hospital has certainly been in agreement with that of the writers to whom reference is made From about thirty to fifty cases of aortic insufficiency developing on the basis of syphilis of the aorta are seen every year, and in almost all these a history of attacks of paroxysmal dyspnea can be elicited on careful questioning, substantiated usually by actual observation of the attacks in the wards³

We have come to feel a certain amount of doubt, however, whether paroxysmal dyspnea is dependent directly on syphilitic lesions of the aorta When one attempts to examine many of the earlier descriptions of syphilitic aortitis, such as the ones of Huchard⁴ and of Dieulafoy,⁵ one finds no statement as to whether the cases showing paroxysmal dyspnea had only syphilitic aortitis, or whether they were complicated by the presence of other lesions, such as aortic insufficiency Of the nine cases reported by Longcope⁶ in which paroxysmal dyspnea was present, all were associated with aortic insufficiency In Lamb's⁷ series

^{*} From the medical clinic of Johns Hopkins Hospital and University

1 Huchard, H *Traite clinique des Maladies du Cœur et de l'Aorte*, Paris, Gaston Doin 2 298, 1899 Dieulafoy, G *Manuel de Pathologie Interne*, Ed 3, Paris, Masson & Cie, 1834, 1901 Longcope, W T *Syphilitic Aortitis Its Diagnosis and Treatment*, Arch Int Med 11 15 (Jan) 1913 Lamb, A R *Syphilitic Aortitis and Aneurysm of the Aorta*, Nelson Loose-Leaf Living Medicine 4 531, 1924 Vaquez, H *Diseases of the Heart*, Trans by G F Laidlaw, Philadelphia, W B Saunders Company, 1924, p 382

2 Coombs, C F *Rheumatic Heart Disease*, New York, William Wood & Co, 1924, p 142

3 We have occasionally seen paroxysmal dyspnea in patients with myocardial disease (without hypertension or valvular defects) due either to syphilis or to arteriosclerosis They do not happen to be included in the group of cases we have studied

4 Huchard (Footnote 1, first reference)

5 Dieulafoy (Footnote 1, second reference)

6 Longcope (Footnote 1, third reference)

7 Lamb (Footnote 1, fourth reference)

of twenty-six cases, in which the clinical diagnosis of simple aortitis was made, that is to say, none had aortic insufficiency or aneurysm, eight cases showed attacks of paroxysmal dyspnea. Five of the entire group had chronic nephritis, apparently with hypertension, and several of the others had either high systolic blood pressures (150 mm of mercury or over) or high diastolic blood pressures (90 mm of mercury or over). It is not stated whether the patients with paroxysmal dyspnea fell into the group with hypertension, and, as we shall see later, it is a matter of considerable importance to the subject under discussion. Hubert⁸ states that in 118 cases of uncomplicated aortitis outspoken cardiac asthma was present in none.

We have attempted to gather some information concerning this question by analysis of our own cases. We have first of all taken from the necropsy records a number of cases that showed definitely the anatomic lesions of syphilitic aortitis. From both the clinical and the pathologic data of these cases, we have ascertained the presence or absence of certain other conditions: aortic insufficiency, myocardial involvement due to other causes, myocardial insufficiency, aneurysm and hypertension (with or without renal involvement). From the clinical records, we have determined whether paroxysmal dyspnea or dyspnea on exertion was present. There was no selection of cases except that we have discarded those in which the data that we sought were not absolutely clear, and we also have omitted cases in which the syphilitic lesions of the aorta were not situated in their characteristic location, namely, at or near the root of the aorta. We wish to emphasize the fact that the cases we have used for study have been ones in which syphilitic aortitis has been definitely proved to be present at necropsy.

The results of our investigation are given in the accompanying table.

*Analysis of Eighty-Two Cases of Syphilitic Aortitis with
Especial Reference to Presence of Dyspnea*

Type of Lesion	Total Number of Cases	Cases Showing Dyspnea on Exertion	Cases Showing Paroxysmal Dyspnea	Cases with Myocardial Insuffi- ciency
Uncomplicated syphilitic aortitis	24	0	0	0
Syphilitic aortitis with aortic insufficiency	28	27	25	26
Syphilitic aortitis with aortic insufficiency and aneurysm of root or arch of aorta	5	5	5	5
Syphilitic aortitis with aneurysm of root or arch of aorta	12	6	4	4
Syphilitic aortitis with hypertension	10	10	5	10
Syphilitic aortitis with extensive scarring of myocardium	2	2	0	2
Syphilitic aortitis with laryngeal obstruction due to tumor	1	0	1	0

⁸ Hubert, G. Zur Klinik und Behandlung der Aortensyphilis, Deutsch Arch f klin Med **128** 317 (Feb) 1919

COMMENT

The table needs but little comment. In none of the cases of uncomplicated syphilitic aortitis, twenty-four in number, was paroxysmal dyspnea present. This symptom occurred in almost all the cases associated with aortic insufficiency, and in a number of those with hypertension. It was also present in a fair proportion of the cases of aneurysm of the root or arch of the aorta without aortic insufficiency. Since it seems apparent, at least from the cases that we have studied, that syphilitic aortitis in itself fails to bring on paroxysmal dyspnea, it is likely that aneurysms in this location produce paroxysmal dyspnea by mechanical compression of the trachea or possibly of the recurrent laryngeal nerve, or because they are associated with myocardial damage of one sort or another. If we except aneurysms, then, the chief conditions that have paroxysmal dyspnea as one of their outstanding symptoms are aortic insufficiency due to syphilitic aortitis and hypertension.⁹ The question arises as to why cases of aortic insufficiency due to syphilis show this symptom and why cases of aortic insufficiency of rheumatic origin do not. It is not altogether surprising, however, that these two conditions should differ clinically, since they differ in other respects, anatomically and in their natural history. On the other hand, aortic insufficiency of syphilitic origin has much in common with hypertension. In both these conditions, one sees anatomically the huge hearts characterized mainly by hypertrophy and dilatation of the left ventricle. We recognize that myocardial insufficiency is a state of functional impairment in which the whole myocardium participates, yet it seems true that in these two conditions, aortic insufficiency due to syphilitic aortitis, and hypertension, it is the left ventricle that seems to bear the brunt of the burden. Clinically, they are the conditions in which Cheyne-Stokes respiration is encountered most frequently, and also those in which sudden attacks of pulmonary edema are most likely to develop, when myocardial failure supervenes, the course is generally rapidly downhill. Why paroxysmal dyspnea should be so frequent a symptom of these two diseases is not clear, since the fundamental cause of paroxysmal dyspnea is not definitely understood.* The recent work of Eppinger and his associates¹⁰ is of interest in this connection. They have presented evidence to show that during attacks of cardiac asthma (paroxysmal dyspnea) there is a striking increase in the circulatory minute volume. They explain the development of paroxysmal dyspnea

⁹ By hypertension we shall mean either chronic nephritis with hypertension or the condition known as essential hypertension.

¹⁰ Eppinger, H., von Papp, L., and Schwarz, H. *Ueber das Asthma Cardiale, Versuch zu einer peripheren Kreislaufpathologie*, Berlin, Julius Springer, 1924.

and pulmonary edema on the assumption that the left ventricle becomes unable to cope with the increased volume of blood brought to it

All the patients with paroxysmal dyspnea (excepting those with tracheal obstruction) have had as a symptom, besides dyspnea on exertion, other gross evidences of myocardial failure. Apparently there are some cases, such as those described by Longcope,⁶ in which paroxysmal dyspnea may develop for months before the usual signs of myocardial failure appear. It does not follow, however, that this symptom may not be a manifestation of myocardial insufficiency, as Longcope has intimated. It is not unusual to see patients suffer from dyspnea on exertion for a long time before gross signs of myocardial failure appear, and in these cases it is generally accepted that dyspnea on exertion is due to myocardial insufficiency.

Our purpose is to point out that, so far as one may judge from a study such as we have made, paroxysmal dyspnea is not a manifestation of uncomplicated syphilitic aortitis. When this symptom is seen in such cases, it is usually due to the presence of aortic insufficiency. We do not mean to imply thereby that paroxysmal dyspnea loses all its diagnostic significance. Undoubtedly, the presence of this striking symptom points definitely to the syphilitic origin of a case of aortic insufficiency, the cause of which might otherwise be obscure.¹¹ But this symptom indicates the presence of syphilitic aortitis not because syphilitic aortitis is directly responsible for the occurrence of paroxysmal dyspnea, but because it leads to the development of a peculiar kind of heart disease. A condition somewhat analogous is carcinoma of the pylorus of the stomach. The symptoms caused by this lesion, though usually characteristic, are dependent in the main on the location of the growth, rather than on the growth itself.

SUMMARY

In eighty-two cases of syphilitic aortitis proved by necropsy to have the characteristic anatomic lesions, paroxysmal dyspnea was present only when associated with aortic insufficiency, hypertension or aneurysm of the root or arch of the aorta. It would seem, therefore, that paroxysmal dyspnea was not a symptom due directly to syphilitic aortitis. Nevertheless, it is an important symptom in the differentiation between aortic insufficiency of syphilitic and of rheumatic origin.

11 There are rare cases of cardiovascular hypertensive disease that lead to the development of aortic insufficiency without any other demonstrable cause being discovered. That is to say, there may be insignificant atherosclerotic changes in the aorta, and there may be no evidence of syphilitic involvement of the aorta, or of rheumatic heart disease. In these patients, paroxysmal dyspnea may occur, and we do not know of any means by which this type of case may be differentiated from those of aortic insufficiency dependent on syphilitic aortitis, associated with cardiovascular hypertensive disease, except by the blood Wassermann reaction.

EVIDENCE OF NERVOUS CONTROL OF LEUKOCYTIC ACTIVITY BY THE INVOLUNTARY NERVOUS SYSTEM *

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The leukocytes, their various activities, their independent life in the circulating blood, and their importance in the human economy have been a subject of medical research ever since the discovery of their existence

Though leukocytes play an important part in all local processes connected with infection and inflammation, they are produced in only one organic system, namely, in the bone marrow of the short bones (vertebrae, ribs, skull) and in the short bones of the hands and feet In times of great need, as for instance during acute general infections, such as pneumonia, leukocytes are also formed in the long bones of the extremities, which usually contain only fatty tissue In studying leukocytosis and the activity of individual leukocytes and especially the cause of the appearance of large numbers of leukocytes of the polymorphonuclear type in such infected areas, an interesting problem presented itself As far as human beings are concerned the well known old theory of chemotaxis, first established by the botanist Pfeffer, is unsatisfactory It may be that in test tubes as well as under the abnormal conditions surrounding experimental work in animals, leukocytes will accumulate around germs, moved by chemotactic processes, but even so the question of the cause of leukocytic migration is not settled as long as the vessels are not injured, as is prerequisite to animal experimentation

Before a description of the details of our studies is given, the problem itself should be made as clear as possible In using the word migration we do not mean the passage of leukocytes from the vessels through their walls into the tissues but rather their movement in the normal circulation to a given point in the circulatory system For instance, we know that in gonorrhea not involving a general leukocytosis, the already existing leukocytes gather in the vessels of the inflamed part and that these leukocytes later appear in the excretions The same migration of leukocytes to areas of inflammation is known to take place in cases of metastatic foci (septicemia), but our problem deals only with the power that impels the leukocytes to migrate from their site of production through the circulation to an infected area and which then

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* Read before the Chicago Pathologic Society Feb 9, 1925

for a time keeps them from the circulation, confined at the site of inflammation

Research in human beings along these lines became possible when it was recognized that a reaction of the leukocytes consists of a sudden displacement of large numbers of these organisms from one part of the body to another

From experiments first carried out by Goldscheider and Jacob¹ it is well known that a drop in the number of leukocytes in the peripheral vessels follows immediately on injection of peptone solution into the circulation. Recent experiments along these lines revealed that almost no leukocytes are present in the peripheral blood, for perhaps ten minutes after the injection of 10 c.c. of a 20 per cent peptone solution and that these leukocytes accumulate in the vessels that are controlled by the splanchnic nerve, particularly those in the liver². Although usually a slight increase of leukocytes in the periphery follows the ingestion of food, certain patients will show a slight drop after drinking milk on an empty stomach. This phenomenon, first observed by Widal³ has been termed "crise hemoclasique". Experiments have shown that during the slight decrease of the Widal test, which was reproduced in animals, and also during the period of the decrease of the leukocyte count in the peripheral vessels, the leukocytes accumulate in the splanchnic region. The last discovery along these lines has been that injections of non-specific albumin preparations, as well as of minute amounts of salt solution, of distilled water and even of air, are capable of producing an immediate leukopenia in the entire periphery⁴. This leukopenia lasts for perhaps thirty minutes if produced by albumin injections and for from five to ten minutes if caused by the introduction of air or physiologic sodium chlorid solution into the skin.

The discovery that acute leukopenia follows the injection of albumin in every human being, normal or diseased, with the exception only of persons afflicted with certain skin diseases, makes it possible to study the reasons for this leukocytic displacement and points the way to ascertaining the cause of leukocytic activity.

It is astonishing, indeed, that the intradermal injection of a nonirritating albumin that does not cause the slightest pathologic change in the cells and tissues surrounding the site of injection should cause a reaction in the entire circulation. This phenomenon consists not only of a local change of the leukocytes in the vessels involved by the injection

1 Goldscheider, A., and Jacob, P. *Ztschr. f. klin. Med.* **25** 373, 1894

2 Mueller, E. F., and Myers, C. N. *Proc. Soc. Exper. Biol. & Med.* **22** 95, 1924

3 Widal, F., Abram, P., and Brissaud, E. *Presse med.* **28** 181 (April 3) 1920

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tion but of a rearrangement of these cells in the entire circulation. Expressed in numbers, the exact loss of leukocytes to the peripheral circulation and their accumulation in the vessels controlled by the splanchnic nerve reaches from 50 to 75 million, these leukocytes are actually moved from one place to another. In discussing such a migration it must be taken into account that leukocytes are not stationary in the body, but rather that they are continually in circulation and that, normally, they are evenly distributed, an equal number of cells being found in equal amounts of fluid serum. It has been proved experimentally that within a period of one hour the total number of leukocytes does not vary so long as the individual keeps quiet and experiences no physical or mental excitement.

The intradermal injection of a mild preparation acts in the manner described. No more than 0.2 c.c. of a solution containing about 4 per cent of albumin is given intradermally, in actual numbers 0.0012 gm of albumin is introduced into the skin where it remains unabsorbed as a deposit during a period of about ten minutes. If the same amount of albumin in the same quantity of fluid is given subcutaneously, intramuscularly or intravenously, no change in leukocytes takes place. Tissue excised shortly after any of the latter modes of injection shows no pathologic involvement, nor does the number of leukocytes vary after the injection. But if, on the other hand, not more than two or three drops of the milk preparation are injected into one or two wheals *within the skin* the leukocyte curve will show the drop mentioned in the foregoing. Expressed in percentage this decrease is not influenced by any leukocytosis or by conditions such as leukemia or chronic leukopenia. In normal subjects the number of leukocytes in the peripheric vessels drops from about 8,000 to 5,000, in cases with leukocytosis (as for instance, in pneumonia and in purulent diseases) a drop from 25,000 to 16,000 is observed. Cases of leukemia are reported and I have seen them when the leukocytes have dropped from 150,000, usually observed in such cases, to 70,000 and 80,000, thus showing that the ratio of the decrease remains approximately the same. The actual numbers of the leukocyte drop in the peripheric vessels in cases of leukemia may be given at from about 100 to 120 million. Cases of leukopenia (as for instance, in pernicious anemia) react to intradermal injections of protein with a decrease from about 5,000 to 1,600.

The amount of fluid injected or its solid content, beyond doubt, is unable to produce of itself any organic change in the body. This is proved by the injection of identical substances in equal amounts into other body tissues. Further proof is seen in the fact that the injection into the derma of air instead of the milk preparation and the application of a new kind of very soft roentgen rays which latter test I have recently

carried out in collaboration with Bucky,⁵ exerts an influence on the skin similar to the stimulation by means of intradermal injections of non-specific albumin. The drop in the leukocyte curve produced by the injection of air and the administration of this radiating energy is

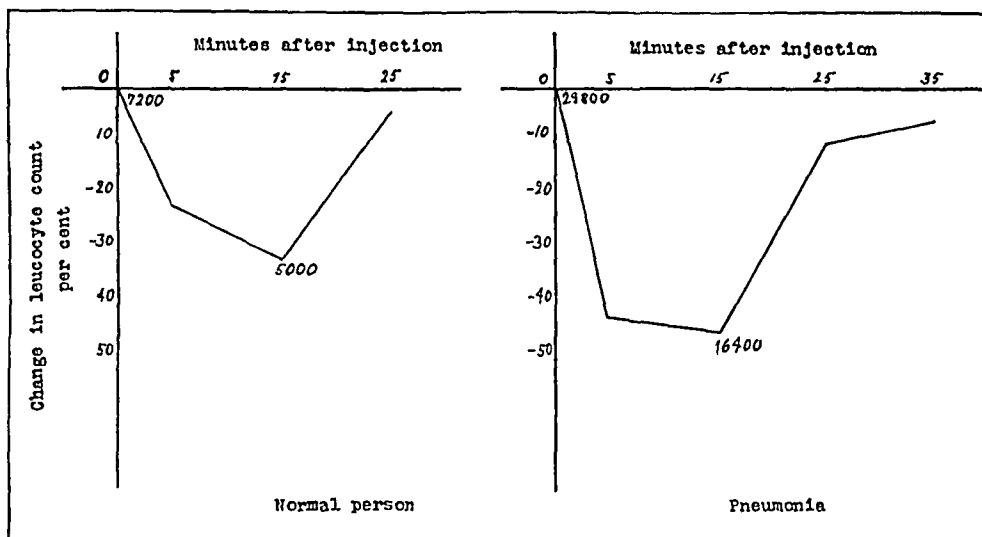


Chart 1—Peripheral leukopenia after intracutaneous protein injections in normal and in pneumonic patient

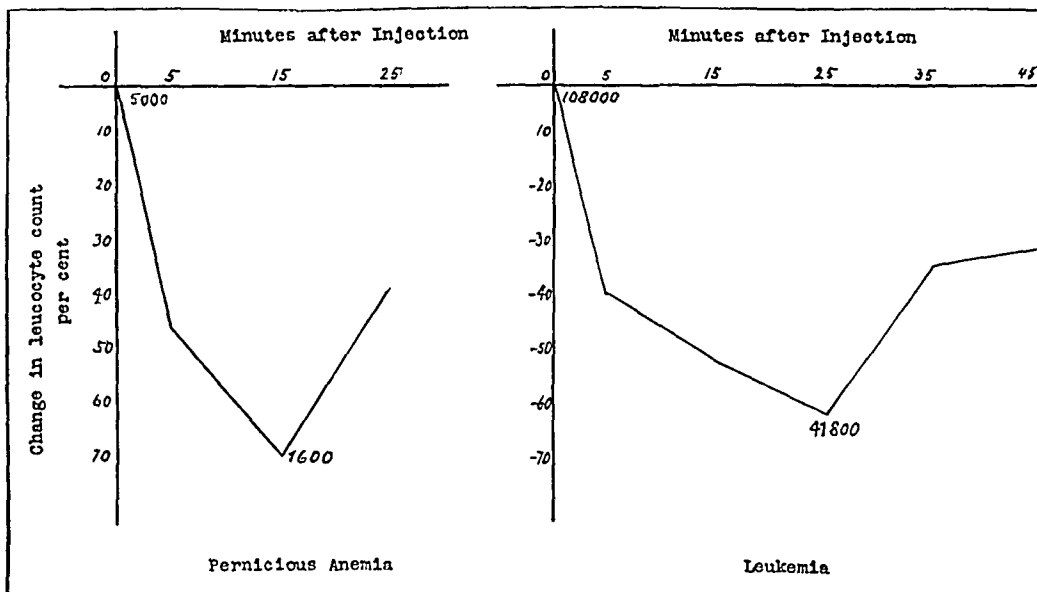


Chart 2—Peripheral leukopenia after intracutaneous protein injection in pernicious anemia in leukemia

smaller and does not last as long, nor does it produce certain focal reactions resulting from intradermal injections of the milk preparation. But a comparison with injections into other tissues and the injection of

⁵ Bucky, Gustav, and Mueller, E. F. Munchen med Wchnschr **72** 883 (May) 1925

air into the derma gives evidence that the injected fluid is not the direct cause of the phenomenon but rather the tissues into which the injection is made

Studies undertaken in the last three years have shown that a close relationship between the skin and the involuntary nervous system, more particularly its parasympathetic part, is responsible for the decrease of leukocytes in the peripheric vessels and for their aggregation in the splanchnic region. By blocking the nerves which carry parasympathetic stimuli to the splanchnic region, i. e., the vasodilators, we were able to demonstrate that it was no longer possible to produce the described changes in the leukocyte curve.⁶ Experiments in human beings have shown that epinephrin and atropin, administered in small doses subdermally, in any part of the body, make it impossible, for perhaps half an hour, to influence the leukocyte count by means of intradermal injections. Our studies show that epinephrin, by increasing the tonus of the sympathetic system, acts precisely the same as atropin, decreasing or paralyzing the tonus of the parasympathetic system. Pilocarpin, which acts on the involuntary nervous system by increasing the action of the parasympathetic, does not change the influence of intradermal injections on the leukocytes. On the contrary, pilocarpin as a rule produces a slight drop in the leukocyte curve, so that if, ten minutes after the administration of pilocarpin, a milk preparation is given intradermally even though the leukocyte count be comparatively low (from 4,000 to 5,000), the intradermal injection causes a still greater decrease to from 2,000 to 3,000, thus proving that the pathways of intradermal stimulation are not disturbed or blocked by pilocarpin.

The decrease of leukocytes following intradermal injections, which actually involves a leukocyte drop in the entire periphery (blood of veins and arteries shows the same decrease observed in the peripheric vessels) and an accumulation of these missing leukocytes in the splanchnic region, is to be based on a sudden change in the vascular system of the splanchnic region produced by parasympathetic stimuli that originate automatically in the human economy after the described skin stimulation.

Thus, it was recognized that the liver and probably also the other blood vessels of the splanchnic region, by means of the described stimuli accumulate and retain the circulating leukocytes during the period of stimulation. The cause of the leukocytes lodging in these vessels, parasympathetically dilated, is entirely unknown. We can only assume that some chemical or electric relationship exists between the wall of a parasympathetically stimulated and dilated vessel and the fluid and the cells circulating in these vessels. The observation of this migration of leuko-

⁶ Mueller, E. F., and Hoelscher, R. *Ztschr. f. d. ges. exper. Med.* **38** 478, 1923, **61** 325, 1924.

cytes into the splanchnic region and their retention in the same has been confirmed by animal experiments. The existence of a close relationship between the vessels and the circulating fluid may be concluded from the following tests. If tertiary syphilitic patients with a negative Wassermann reaction are given an intradermal injection of a milk preparation, then serologic reaction will turn positive for two or three days. This experiment, repeated several times, always gave the same result thus demonstrating that changes in the vascular system are able to influence the colloidal condition of the serum. We are not sure whether the vessels themselves in their state of dilation are able to produce this change in the colloidal condition of the serum, or whether both the vascular and the serologic changes are attributable to some other common cause. Recent studies by Embden and Freundlich⁷ on the nature of the phenomenon of sudden peripheral leukopenia have added to our knowledge of its origin.

In patients in whom a so-called sympathectomy has been performed, the intradermal injection of a milk preparation into the derma of such an extremity no longer results in a decrease of leukocytes. The term sympathectomy is incorrect. The actual operation consists in severing the nerves accompanying the large vessels or in excising a ganglion. If the nerves accompanying the main vessels of the extremities were entirely cut off we would not then state that a sympathectomy had been performed, yet every fiber of the vasoconstrictors and of the vasodilators has been thus disconnected.

It does not pertain to the theme of this paper to go into details about the vascular control of an extremity in which the large fibers of the involuntary nervous system have been cut off, but it may be mentioned that the local control of the peripheral vessels is still in effect, even though the balance is visibly disturbed. But, as stated before, intradermal injections into any part of the skin of such an extremity no longer cause a leukocyte fall.

Thus, it is shown that, after the intradermal injection, the large fibers of the involuntary nervous system play an important part in conducting the stimulus originated in the skin to the vessels of the splanchnic region.

The following discovery, also described by Embden and Freundlich in a confirmation of our previous statements, is of great interest. If, after operative disconnection of the nerves accompanying the large vessels of an extremity, the subject is given an intradermal injection into any part of his body, outside of this extremity, then the leukocyte drop will occur in all the peripheral vessels with the surprising exception of the extremity in which the nerves have been severed. This reveals that

⁷ Embden and Freundlich, H. Munchen med Wchnschr, to be published

the splanchnic region is not the only factor active in originating the described phenomenon of the leukocyte curve. If it were merely the task of the splanchnic region to retain the leukocytes, there would be no reason why leukocytes which without difficulty enter and leave that particular extremity should not turn into the splanchnic vessels. If, after the severing of the nerves in one extremity, this particular extremity no longer participates in the phenomenon, then, clearly the part played by this extremity has not been merely a passive one. An active participation in the reaction must have taken place which becomes impossible on disconnection of nerve conductivity. We may therefore conclude that during the period of actual peripheral leukopenia following intra-dermal injection, both the skin and the splanchnic region share in the production of the phenomenon. The action of the skin must account for the hitherto unexplained influence of the skin vessels themselves on the leukocytes. This influence must be the reverse of the influence of the splanchnic vessels during the leukocyte fall. The splanchnic vessels would seem to attract and the skin vessels to repel the leukocytes thus influencing their numerical presence. We do not wish to discuss any theoretic possibilities as to how this influence acts, we merely report actual observations. We know that the splanchnic region receives parasympathetic stimuli, the vessels are dilated to a certain degree. The resulting change of the walls and their permeability is somehow related to this dilatation. The leukocytes accumulate, and this accumulation is based on changes in the parasympathetic overbalance of the vessels controlled by the splanchnic nerve, this being evident from the fact that the accumulation lasts only for the period of this parasympathetic overbalance.

The action of the skin vessels is just the reverse as far as the leukocytes are concerned. It was observed that a decrease of the actual number of leukocytes no longer obtains if the nerves are severed and the assumption is warranted that the balance of these vessels is disturbed.

To further study the action of the skin vessels during the leukocyte decrease the following tests were performed. Friction or heat was applied to a part of the skin until the area appeared red, examination revealed that the number of leukocytes had increased 30 per cent in this artificially congested area. This observation is readily explained both friction and heat produce dilatation, the immediate cause of which is a reaction of the vasodilator, resembling the reaction of the vessels of the splanchnic region to parasympathetic stimuli. The effect of dilatation on the leukocytes is the same in every region of the body they accumulate progressively. This simple experiment gives evidence, especially in connection with the phenomenon described above that vasodilatation by active nerve action causes a local aggregation of leukocytes.

Another simple experiment was carried out. If small amounts of very dilute solutions of epinephrin (1:100,000) are injected subdermally or intradermally, the vessels in the adjoining region show a low leukocyte count that differs from 30 to 40 per cent from that obtaining in other regions of the body. These experiments must be made carefully. If too much epinephrin is given the vessels will be closed and neither leukocytes nor erythrocytes will be found. However, with the correct concentration—and this varies in different individuals—the surprising fact develops that the leukocytes show a decrease and that this decrease affects only the polymorphonuclear type. The same decrease of leukocytes will be noticed if cold is applied to the skin. A decrease of polymorphonuclear leukocytes will be evident in the affected area, while erythrocytes and lymphocytes remain unchanged. We wish to call attention to the fact that every decrease of leukocytes referred to in this article affects only the polymorphonuclear type, while in from 70 to 80 per cent of the cases examined, the lymphocytes are not influenced and their numbers not affected. Considering only the proportional figures, the lymphocytes may seem to have increased, but by calculating the absolute value, the lymphocyte curve and the curve of the red cells will be a straight line while the leukocyte curves show a marked dip.

The following conclusions are drawn. If the normal balance of the vasodilating and vasoconstricting nerves is disturbed the number of leukocytes actually present will be found to vary in direct ratio to the overbalance. If the disturbance of the balance of the vasoconstricting nerves is deflected to a sympathetic overbalance, a local leukopenia will immediately result. If the deflection is toward the parasympathetic, and the normal condition of a particular vascular region is overruled by the vasodilating nerves, an immediate leukocytosis will manifest itself and will last as long as this particular disturbance of the vasodilating nerves is effective. This rule, which applies to every region of the body, may be established as an indicator of the balance of the vasocontrolling nerves, and it may lead to evidence of a nervous control of leukocytic activity of which the leukocyte fall is only one feature. It is definitely established that during the time of the phenomenon the entire skin shows an overbalance of the sympathetic nerves over the parasympathetic. Moreover, we know that the liver and the vessels of the splanchnic region show a contrary fixation when the parasympathetic, vasodilating nerves prevail. If that is the case, the splanchnic region, as represented in one part by the liver, and the periphery, as represented in one part by the skin, forms two large systems, balancing each other as far as the nervous control is concerned and holding in balance also the number of leukocytes in their vessels. Furthermore, the skin as a part of the periphery and the liver as a part of the splanchnic region together form

one great entity that is probably controlled by one and the same nervous action

The last assumption is still unproved. From the mentioned observation we merely know that while the splanchnic region receives parasympathetic stimuli and acts in a parasympathetic overbalance, the skin simultaneously receives sympathetic stimuli and acts in this direction. If periphery and splanchnic region regulate each other and are actually controlled by one mutual nervous action, a reversion of these two stages in both regions must be possible. We have succeeded in demonstrating this reversion.

We shall confine ourselves to a statement of the principal results. If in diabetic patients an abnormally low blood sugar level due to an overdose of insulin is reached, symptoms of so-called insulin shock occur. Insulin shock, as is known, manifests itself as a feeling of weakness, dizziness and trembling of the extremities, then profuse perspiration sets in and the feeling of weakness increases until the patient reaches an alarming condition.

The peripheral symptoms of insulin shock, especially the profuse perspiration of a watery fluid, indicate an overbalance of parasympathetic innervation resulting in dilatation of the vessels and in an increase of endothelial permeability. (This watery perspiration should be clearly distinguished from the perspiration of a more viscid fluid, the product of sympathetically stimulated and functioning sweat glands.) A careful investigation of the number of leukocytes during insulin shock—a condition that has been observed only twice among a large number of diabetic patients treated with insulin—leads to the remarkable discovery that the leukocytes increase with the lowering of the blood sugar. If the blood sugar is lowered beyond a certain limit, for instance, to 50 per cent of the normal figures, the leukocytes increase rapidly, reaching numbers never observed in fasting patients. In the two cases of insulin shock under observation the leukocytes reached 28,000 and 19,000. In each instance this rise took place within less than fifteen minutes.⁸ In both cases the patients had to be given immediate treatment with glucose, to prevent further danger. Then another surprising observation was made. In the very moment in which the patients received their glucose the leukocytes immediately decreased. Glucose was administered by mouth only 5 gm. was given in 100 c.c. of water. In less than ten minutes the leukocytes had decreased to 7,000, the level that obtained prior to insulin treatment.

Simultaneous with the decrease of leukocytes all the alarming symptoms produced by the parasympathetic overbalance in the entire periphery were checked, thus proving complete parallelism between the

⁸ I observed these cases in the department of metabolism of the Vanderbilt Clinic.

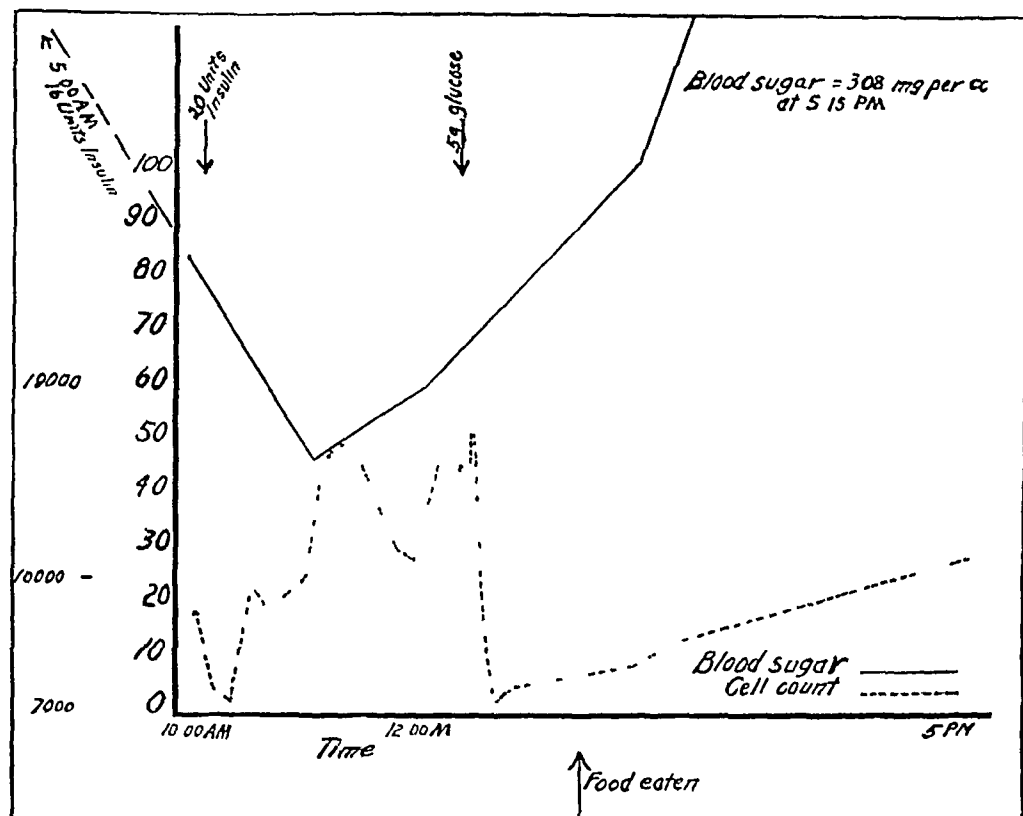


Chart 3—Relation of leukocyte count to insulin shock

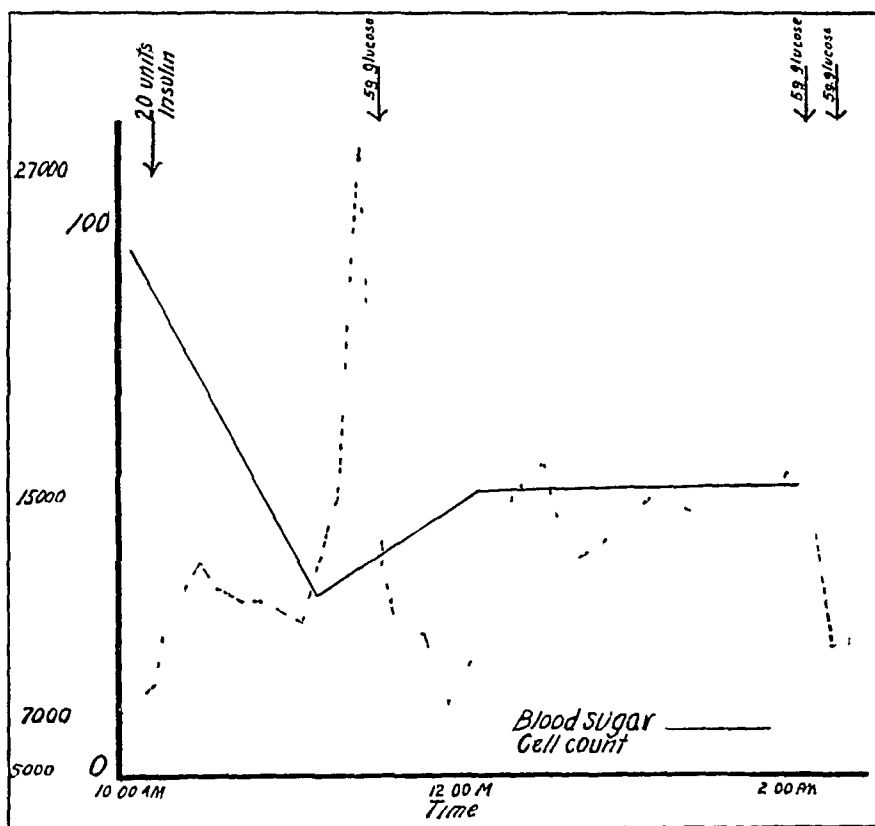


Chart 4—Relation of leukocyte count to insulin shock

parasympathetic overbalance in the periphery and the leukocyte curve. That a sympathetic overbalance in the splanchnic region exists at the same time has been shown by more complicated experiments which will be reported later.

As it has not been possible to duplicate in human beings the observations we made accidentally in the two cases quoted, we have performed tests in rabbits, using high doses of insulin and have demonstrated that in 80 per cent of the rabbits so treated the leukocytes in the ear vein increased markedly (about 20,000), during the time of the low blood sugar level (about 30 per cent). This phenomenon did not occur uniformly in all rabbits but then these animals are not diabetic, and we know from experience in human beings that insulin shock is unusual in nondiabetic subjects. This observation may offer an explanation of varying results in animal tests. A number of animals, however, showed a distinct parallelism with the findings in human beings, reacting with a decrease of leukocytes to the intraperitoneal injection of glucose which reached the original level in from five to ten minutes.

It is concluded from the foregoing that if the blood sugar is suddenly lowered beyond a certain level, then the skin as a part of the periphery receives parasympathetic stimuli and the result is a dilatation of the vessels, increased permeability, profuse perspiration, increase of leukocytes and the clinical symptoms of insulin shock. The splanchnic region at the same time receives sympathetic stimuli, the nature of which is only partly understood. (The experiments of Claude Bernard have already proved that an abnormal decrease in blood sugar leads to sympathetic stimulation of the liver region the result of which in one particular is to increase the formation of glucose.) These observations practically represent the reversion of the disturbance of balance in the involuntary nervous system which obtains during the period of the so-called leukocyte drop. If in this reversed condition of parasympathetic overbalance in the entire periphery and of sympathetic overbalance in the splanchnic region glucose is given by mouth, the original balance is immediately restored.

The latter observation of the restoration of the balance as affected by a change in blood chemistry, i. e., lowering of the blood sugar, tends to show that nerve action plays a regulating part. If one considers both phenomena, the leukocyte drop and the insulin shock with its peripheral leukocytosis, and if one further considers that the possibility of reversing the disturbance of balance during the leukocyte drop has been demonstrated, the assumption gains in strength that the periphery as represented by the skin and the splanchnic region as represented by the liver are controlled by one nerve center. This nerve center and its anatomic location are unknown. It may consist of one ganglion, it may be a large nervous system, the physiologists will have to locate it. From studies

with the so-called sugar center in the medulla we know that the latter acts in close relation to the center and we furthermore know that a sudden irritation of the solar ganglion produces similar manifestations, as an insulin shock. But this leads us beyond the scope of this article.

A mutual nervous control of the periphery and of the splanchnic region may lead to absolutely new conceptions in some fields of medicine. Other studies along these lines will be published in the near future. Our problem has been to ascertain the cause of leukocytic activity, or more particularly of the migration of leukocytes. Investigation of the leukocyte drop and of its reversion has demonstrated that acute peripheral leukopenia and acute peripheral leukocytosis always correspond to leukocytosis of leukopenia, respectively, in the splanchnic region, depending on the nervous control. Where parasympathetic stimuli predominate in the vascular system, there the leukocytes will accumulate, while an overbalance of sympathetic stimuli produces a decrease of leukocytes in this region. Both processes originate in the involuntary nervous system, the migration of the leukocytes being but a sequel. There is no evidence to support the fact that the leukocytes in their migration are subject to passive transportation only. It is quite possible that the leukocytes actively participate in the described migrations, viz., the accumulation in the periphery or in the splanchnic region. Many theories have been conceived but no facts are established. Whether or not the leukocytes individually take an active part in this migration is not certain. On the other hand, it has been definitely established herewith that leukocytic activity depends on a nerve action. The involuntary nervous system and its branches control the number of leukocytes present at one time in the various regions of the body. Since it is possible by artificial irritation and stimulation of the involuntary nervous system to produce an accumulation of leukocytes in the periphery as well as in the splanchnic region, it is evident that the involuntary nervous system is a dominating factor in the production of this phenomenon. This fact will remain, whether or not new discoveries lead to acceptance of the theory of passive transportation of the leukocytes or of an active response to a stimulus provided by the involuntary nervous system, or of a difference in the electric charge of the leukocytes and walls of the vessels as productive of leukocytic activity. Should the latter possibility, i. e., a difference in the electric charge of the leukocytes and walls of the vessels, obtain, it would only be a sequel to the involuntary stimulus taking effect in that particular vascular region. To future studies may be left the task of developing the new findings and of establishing and completing on the basis of these data entirely new conceptions of focal reaction, inflammation and leukocytic activity in pathologic conditions.

SUMMARY

The number of leukocytes found in any vascular region of the body depends on the balance of the involuntary nervous system in this particular region. The leukocytes will be evenly distributed so long as the involuntary nervous system, vasodilators and vasoconstrictors are in normal balance. The uniform distribution changes immediately if there is an overbalance in either direction. Such an overbalance never takes place in the entire body. If large areas are involved, peripheral and splanchnic regions balance each other. An overbalance of the sympathetic, vasoconstricting portion causes local leukopenia, while overbalance of the parasympathetic, vasodilating part causes leukocytosis. Nervous action is always the primary cause of leukocytic activity as far as accumulation and decrease are concerned, even though the leukocytes are in no way directly connected with either the walls of the vessels or with the vasocontrolling nerves of the involuntary nervous system. This knowledge may furnish a new link connecting immunity and body resistance (of which the leukocytic activity is only one part) with the teachings of pathology and physiology in the human economy.

INTRADERMAL SALT SOLUTION TEST IN CARDIAC DISEASE IN CHILDREN ¹

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In 1923 McClure and Aldrich¹ reported that when 0.2 c c of an 0.8 per cent aqueous solution of sodium chlorid was injected intradermally in children, the resulting elevation disappeared or became impalpable much sooner in edematous patients than in certain control patients without edema. Shortening of the disappearance time in edematous patients, while most marked in regions of palpable edema, was also found, to a less degree, in areas in which pitting could not be demonstrated. This report included three cases of children with cardiac disease, in each of which the disappearance time was shorter in the leg than in the arm. In a subsequent paper the same authors² reported the results of the application of the test in sixteen children having nephritis, with generalized edema. They pointed out that the decreased disappearance time found in remotely separated regions of the body in the same subject could be explained on the assumption that a general intoxication so altered the tissues as to increase their avidity for water. They concluded that the test was of considerable aid in prognosis in this type of case, since a diminution of disappearance time preceded the onset of palpable edema, while an increase of time was a forerunner of its departure.

Baker³ applied the test to scarlatinal and diphtheric patients and found a decrease in disappearance time, paralleling the severity of the intoxication. Harrison⁴ tested children with lobar pneumonia, and determined that the disappearance time was constantly diminished, slowly returning to normal during convalescence, she suggested that this indicates a persistent intoxication of the tissues.

Cohen⁵ presented evidence indicating that the intradermal salt solution test may serve as a means of determining the level of adequate

* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital, Chicago.

1 McClure, W. B., and Aldrich, C. A. Time Required for Disappearance of Intradermally Injected Salt Solution, *J. A. M. A.* **81** 293-294 (July 28) 1923.

2 Aldrich, C. A., and McClure, W. B. The Intradermal Salt Solution Test, II, Its Prognostic Value in "Nephritis" with Generalized Edema, *J. A. M. A.* **82** 1425-1428 (May 3) 1924.

3 Baker, W. J. Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, *J. A. M. A.* **83** 1566-1567 (Nov 15) 1924.

4 Harrison, Jeanette. Intradermal Salt Solution Test in Lobar Pneumonia in Children, *J. A. M. A.* **84** 1258-1259 (April 25) 1925.

5 Cohen, M. B. The Intracutaneous Salt Solution Test. Preliminary Report of a Simple Method for Determining the Efficiency of the Circulation in the Extremities, *J. A. M. A.* **84** 1561-1562 (May 23) 1925.

circulation in local vascular disturbances of the sort that lead to gangrene. He also used the test in two cases of cardiac decompensation in which he found the disappearance time much more decreased in dependent parts of the body than elsewhere.

A survey of the previously demonstrated value of the intradermal salt solution test led to its adoption for the study of cardiac disease in children, particularly with reference to decompensation edema and to prognosis.

CLINICAL MATERIAL

Forty-four children in the cardiac ward and three outpatients, of ages ranging from 4 to 12 years, were included in this study, which extended over a period of ten months. Except for one case of acute ulcerative endocarditis, the diagnosis in all was acute or chronic rheumatic heart disease, or the closely associated conditions of acute rheumatic fever and chorea.

TECHNIC

The standard technic of McClure and Aldrich was used in performing the test. The sites most commonly used were the volar surface of the forearm and the outer or inner posterior aspect of the calf. Two-tenths cubic centimeter of an 0.8 per cent aqueous solution of sodium chlorid was injected intradermally under aseptic precautions. Two wheals approximately 2 cm apart were found to be more satisfactory than one in determining the end-point in nonedematous regions, since the "valley" between two elevations was more easily palpated than was a single elevation. The end-point was easily determined in regions of pitting edema. When the disappearance time was normal or nearly so, differences of several minutes were considered within the limit of subjective error.

The tests were made daily or at intervals of a few days or weeks, depending on the severity of the case, and clinical observation of the cardiac condition was noted at the time.

CLASSIFICATION OF CASES

After some experience with the method it became apparent that the cases of cardiac disease fell into four groups with respect to the disappearance time of intradermally injected salt solution. In the first group the time of disappearance was normal over the entire period of weeks or months in which the test was performed, i. e., it remained constantly above fifty minutes in both arm and leg. Figure 1 represents a case of this type.

In the second group (Fig. 2), the disappearance time in the leg was much reduced, while that in the arm remained normal or nearly

so, until the edema ascended to the upper regions. Clinically these patients had pure cardiac decompensation, with edema mainly in the dependent parts of the body.

In the third group (Fig 3), there was a persistently lowered and nearly equal disappearance time in arm and leg, these patients died without becoming edematous in the manner of ordinary cardiac decompensation. In the fourth group (Fig 4), the disappearance time curves, in certain periods, resembled those of the third group, becoming modified to approach those of the second group with the advent of cardiac decompensation.

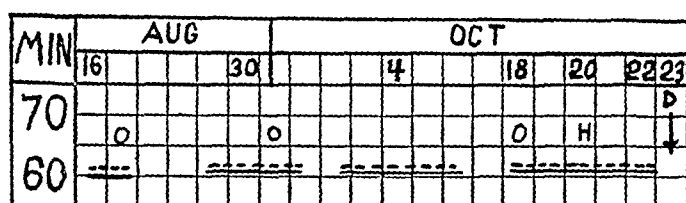


Fig 1—Group 1 solid line, disappearance time in arm, broken line, in leg, points above 60, more than sixty minutes, O, registered as outpatient, H, admission to hospital, D, death

Table 1 shows the distribution of the cases of the four groups according to the chief clinical diagnosis. Each group will be discussed separately.

TABLE 1—Classification of the Four Groups of Cases According to Diagnosis

Group	Acute Endocarditis	Chronic Endocarditis	Acute Pericarditis	Adhesive Pericarditis	Acute Rheumatic Fever	Chorea	Total Number of Cases
1 Normal time	0	12	1	2	2	4	21
2 Decompensated	0	5	3	4	0	0	12
3 Toxic	3	2	1	3	0	0	9
4 Combined	0	2	1	2	0	0	5

NORMAL DISAPPEARANCE TIME IN CARDIAC AND ALLIED DISEASE

Twenty-one patients showed no lowering of disappearance time. Fifteen of these, from a history of rheumatism or previous cardiac decompensation, and from clinical examination, were determined to have organic heart disease, but were well compensated. Several were up and about in the ward, and three were outpatients attending school. All of the cases of chorea and acute rheumatic fever and one case of acute pericarditis fell in this group having normal disappearance time.

The patient whose disappearance time curves are represented in Figure 1 had chronic rheumatic endocarditis. He was well compensated, attending school, and showed a normal disappearance time, whenever tested, over a period of two months. The patient then devel-

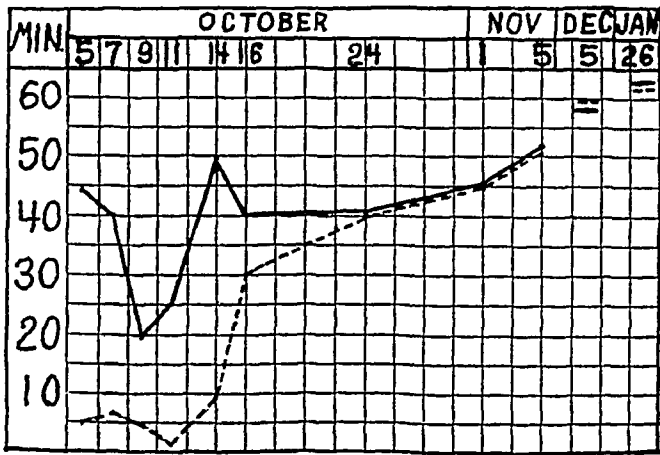


Fig 2—Group 2 solid line, disappearance time in arm, broken line, in leg, points above 60, more than sixty minutes

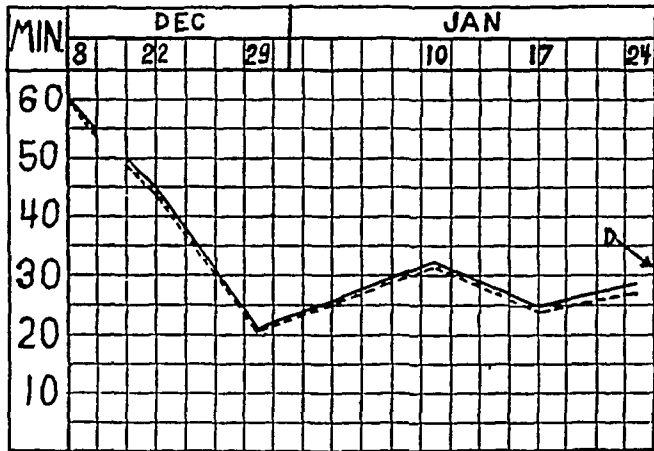


Fig 3—Group 3 solid line, disappearance time in arm, broken line, in leg, D, death

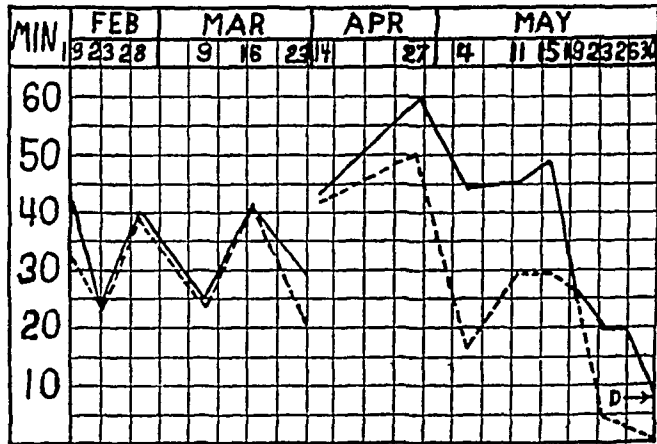


Fig 4—Group 4 solid line, disappearance time in arm, broken line, in leg, D, death

oped tachycardia, was admitted to the hospital, and died at the end of three days, probably of myocardial failure, without the advent of clinical evidence of decompensation. Disappearance time remained normal until death.

TABLE 2—Cardiac Decompensation

Case, Age	Date, 1924	Forearm		Calf		Urine	Clinical Notes
		Pal- pable Edema	Disappear- ance Time*	Pal- pable Edema	Disappear- ance Time*		
1 6 years	10/ 5	0	44 min	++	5 min	Albumin + Casts +	Admitted to hospital, dyspnea, slight cyanosis, large liver, ascites
	10/ 7	0	40 min	++	7 min		Left hydrothorax
	10/ 9	+	20 min	++	5 min	Albumin + Casts +	Increased dyspnea
	10/11	+	25 min	++	1½ min		Decreased ascites
	10/14	0	49 min	+	8 min		Decreased dyspnea
	10/16	0	40 min	+	30 min	Albumin +	Decreased dyspnea
	10/24	0	39 min	0	38 min		Minimal ascites
	11/ 1	0	46 min	0	45 min		No ascites or dyspnea
	11/ 5	0	52 min	0	51 min	Albumin +	In bed, no dyspnea
	12/ 5	0	56 min	0	60 min		
	1925						
	1/26	0	60 min +	0	60 min +		Up part of day
	2/25	0	60 min +	0	60 min +		Up and about
	4/ 1	0	51 min	0	51 min		Home, clinical diagnosis chronic endocarditis, mitral stenosis
2 9 years	2/15	0	50 min	++	18 min		Dyspnea, cyanosis, enlarged liver, sacral edema
	2/17	0	54 min	++	23 min	Albumin +	No dyspnea or cyanosis
	2/19	0	60 min +	+	28 min		No edema
	2/23	0	60 min +	+	33 min		
	2/28	0	60 min +	0	50 min		Bed rest
	3/11	0	60 min +	0	60 min +		
	3/30	0	60 min +	0	42 min		
	4/14	0	60 min	0	60 min +		Up and about
	5/ 4	0	58 min	0	58 min		Home, clinical diagnosis mitral endocarditis and stenosis, adhesive pericarditis?
3 11 years	1924						
	11/ 8	0	57 min	++	18 min	Albumin + Casts 0	Admitted to hospital, dyspnea, enlarged liver, edema of feet
	11/13	0	44 min	++	16 min	Albumin +	Continued dyspnea
	11/15	+	25 min	+++	6 min		Ascites
	11/19	++	20 min	+++	4 min		Face puffy, increased ascites
	11/25	Upper Arm 0	24 min	+++	1 min	Albumin + Casts +	Face puffy, ascites +++, scrotal edema
		Forearm +++	1 min				
	11/28	Shoulder 0	20 min	++++	10 sec		Marked dyspnea and cyanosis, impending heart failure
		Upper Arm ++	45 sec				
	11/30	Forearm +++	30 sec				Died, clinical diagnosis adhesive pericarditis and chronic endocarditis

*In this and the succeeding tables, 60 min + in this column means more than sixty minutes, elsewhere, + means slight, ++, moderate, etc

DISAPPEARANCE TIME IN CARDIAC DECOMPENSATION

Chronic endocarditis, acute pericarditis and chronic (adhesive) pericarditis were about equally represented in this group of twelve cases in which, at some time during the period of observation, cardiac decompensation with edema was present. Table 2 gives data on three cases of this kind, one of which, Case 1, is represented in Figure 2. While the disappearance time in the edematous legs was markedly reduced from the onset of decompensation edema, the time in the non-edematous arms remained normal or nearly so until edema ascended to the upper parts of the body. In these patients edema of the face never preceded that in the lower regions, and often did not occur even in the presence of an otherwise generalized edema. In Case 3 in Table 2, a striking regional difference in disappearance time is shown, November 25, the time was much less in the dependent, edematous forearm than in the slightly edematous or nonedematous upper arm.

Decrease in disappearance time did not precede other clinical evidence of impending decompensation constantly enough to make the test of value in predicting a break in compensation in cases of this type.

GENERALIZED OR "TOXIC" TYPE

This interesting group of nine patients, three of whose records are shown in Table 3, and one, Case 3, in Figure 3, included three cases of acute endocarditis and one case of acute pericarditis. The others were diagnosed chronic rheumatic heart disease. Seven of these children died during the course of observation, two were taken from the hospital and lost track of.

This group exhibited symptoms, signs and necropsy findings of marked valvular lesions, fibrinous, effusive or adherent pericarditis, or a combination of these, considerable cardiac hypertrophy, anemia and undernourishment, sometimes jaundice and fever, and lack of improvement after long rest in bed. In some there was a history of previous decompensation.

Disappearance time was decreased about equally in arm and leg over considerable periods of time, though edema, when present at all, was always minimal and then frequently occurred first in the face or in the sacral region. Later, moderate ascites or scrotal edema sometimes developed but edema of the legs was absent or minimal. These children did not show clinical evidence of decompensation at the time of death, which resulted from either myocardial failure or pulmonary complications.

The nearly equal diminution in disappearance time in arm and leg in this group resembled the results obtained by Aldrich and McClure² in cases of parenchymatous nephritis, but in our cardiac cases the urine either was normal or contained only small amounts of albumin (with

TABLE 3—Generalized, or Toxic, Type

Case, Age	Date, 1925	Forearm		Calf		Urine	Clinical Notes
		Pal- pable Edema	Disappear- ance Time	Pal- pable Edema	Disappear- ance Time		
1 10 years	1/19	0	60 min +	0	60 min +	Normal	Precordial pain, pallor, hemoglobin 60% (Tallquist), pericardial and thoracic effusion normal blood chemistry
	1/24	0	41 min	0	30 min	Albumin + Leukocytes ++	Slight dyspnea, normal
	2/ 2	0	54 min	0	53 min		No dyspnea, less pericardial and pleural fluid
	2/13	0	31 min	0	22 min	Normal	Dyspnea, cyanosis and moderate fever
	2/17	0	23 min	0	22 min	Normal	Vomiting, Cheyne Stokes respiration
	2/18						Died, necropsy adhesive pericarditis, healed rheumatic endocarditis, passive congestion of the kidneys
2 8 years	1924 11/ 1	0	49 min	0	48 min		Pallor, emaciation moderate fever, palpable liver and spleen, hemoglobin 70% (Tallquist)
	11/13	0	34 min	0	42 min	Normal	
	11/21	0	27 min	0	26 min		Dyspnea, fever, sacral edema, ascites, spleen larger, hemoglobin 45%, red blood cells, 3,000,000
	11/28	0	34 min	0	33 min	Normal	Right hemiplegia (embolic)
	12/ 2	0	20 min	0	33 min	Normal	Fever, less dyspnea, no ascites
	12/12	0	29 min	0	28 min		Hemoglobin 35% (Dare)
	12/23	0	28 min	0	26 min		Marked pallor, petechial hemorrhages
	1925 1/ 5	0	46 min	0	26 min		Prostration and continued fever
	1/14						Died, necropsy no edema, thrombo-ulcerative endocarditis, anemic infarcts and lymphocytic infiltration of kidneys
3 9 years	1924 9/ 1	0	49 min	0	60 min		Dyspnea, pallor, enlarged liver
	9/23	0	60 min	0	60 min		No dyspnea
	10/ 7	0	60 min +	0	60 min +		Up part of day
	10/23	0	60 min	0	60 min +		
	11/10	0	60 min +	0	60 min +		Up all day, home November 19
	12/ 6						Returned to hospital on account of vomiting at attacks
	12/ 8	0	60 min	0	60 min		
	12/22	0	45 min	0	43 min	Albumin + + Casts 0	Face puffy
	12/29	+?	22 min	+	21 min	Albumin + + +, casts 0	Cyanosis, pericardial friction rub
	1925 1/ 5	0	40 min	+	26 min	Albumin +	Scrotal edema
	1/10	0	32 min	+	31 min	Albumin +	No facial or scrotal edema
	1/17	0	25 min	+	24 min	Normal	Recurrent facial edema
	1/24	0	28 min	+	26 min	Albumin + + +, casts 0	Extreme pallor, dyspnea irregular pulse, normal blood chemistry
	1/25						Died, clinical diagnosis chronic pericarditis and endocarditis

exception of in Case 3, Table 3) and a few casts, red cells being absent. The nitrogenous elements of the blood, when determined, were within normal limits. Necropsy, in the several cases in which it was permitted, confirmed the diagnosis of cardiac disease, the kidneys were usually passively congested but otherwise normal.

From the fact that all but two of these patients, in whom there was a generalized decrease in disappearance time, died during the period of observation, it would appear that the intradermal test is of considerable confirmatory value in rendering an unfavorable prognosis in this type of cardiac case.

COMBINED DECOMPENSATION AND TOXIC TYPE

Five children who had chronic rheumatic heart disease or acute pericarditis demonstrated during certain periods of their course an equal shortening of disappearance time in arm and in leg. The records of three of these are given in Table 4, and of one of these, Case 3, in Figure 4. Edema was either absent or slight and confined to the face or the sacral region, sometimes there was moderate ascites. As an intermediary or more often as a terminal event, cardiac decompensation with edema occurred, and the disappearance time changed to the type described for the decompensation group, *i. e.*, it became much less in the edematous leg than in the nonedematous or slightly edematous arm.

In two of the patients, tests were performed from two to five hours after death, and the time of disappearance, in regions of pitting edema, was found to be short—about the same as it had been during life.

These children resembled those of the preceding toxic group. They were clinically severe cases of cardiac disease, and unresponsive to treatment, death occurred in all. Clinical or necropsy findings, or both, established the presence of cardiac disease and absence of kidney involvement, except for chronic passive congestion, and in Case 2 cloudy swelling.

COMMENT

The decreased disappearance time of the intradermally injected salt solution probably indicates an increased water affinity of the adjacent tissues. This increased water affinity doubtless depends on an abnormal state of the tissues.

By means of the intradermal salt solution test those cardiac cases which exhibit a decreased disappearance time are separated into two groups from the standpoint of location of this tissue disturbance. In the first group there is a localized tissue disturbance, chiefly at the site of edema, and a definite cardiac decompensation, in the second group, a generalized tissue disturbance and no cardiac decompensation.

TABLE 4—Combined Type

Case, Age	Date, 1924	Forearm		Calf		Urine	Clinical Notes
		Pal- pable Edema	Disappea- ance Time	Pal- pable Edema	Disappea- ance Time		
1 8 years	8/24	0	50 min	0	60 min +		Bed rest, no dyspnea
	9/16	0	55 min	0	54 min		
	9/27	0	39 min	0	60 min		
	10/16	0	60 min	0	45 min		Edema over sacrum
	10/20	0	48 min	0	35 min		
	10/24	0	41 min	0	39 min		
	10/27	0	49 min	0	47 min		Dyspnea, rapid pulse, sac- ral edema
	11/ 3	0	28 min	+	18 min		Puffiness of face
	11/ 8	0	23 min	+	11 min	Normal	Enlarged liver, ascites ?
	11/13	0	48 min	++	10 min		Ascites and vulval edema
	11/25	0	37 min	++	11 min	Normal	Right hydrothorax
							Puffy face, dyspnea, cyano- sis
	11/28	0	44 min	++	6 min		Precordial pain
	12/ 2	+	32 min	+++	1 min		Marked dyspnea
	12/ 8	+	21 min	+++	20 sec		Died, clinical diagnosis
	12/ 9						adhesive pericarditis and chronic endocarditis
2 12 years	10/ 1	0	45 min	+	5 min	Albumin ++ Casts +	Dyspnea and enlarged liver
	10/ 5	0	24 min	+	8 min		Dyspnea
	10/ 7	0	53 min	+	15 min	Albumin +	No dyspnea
	10/ 9	0	50 min	0	27 min		Jaundice and fever
	10/14	0	60 min +	0	43 min	Albumin +	Decreased jaundice
	10/22	0	60 min +	0	56 min	Albumin ++	No jaundice, recurrent fever
	10/27	0	32 min	0	30 min		Gain in weight
	11/ 1	0	43 min	0	28 min		Subicteric
	11/ 3	0	32 min	0	30 min		Jaundice, no dyspnea
	11/ 8	0	36 min	0	26 min	Albumin +	Jaundice
	11/10	0	38 min	0	37 min	Normal	Jaundice decreased, ascites?
	11/19	0	31 min	0	29 min	Albumin +	
	11/28	0	46 min	0	50 min	Normal	No jaundice, up part of day
	12/ 2	0	36 min	0	35 min		Up most of day
	12/12	0	56 min	0	54 min		Acute pharyngitis
	12/29	0	40 min	0	38 min	Albumin +	
	1925						
	1/14	0	50 min	0	49 min	Normal	Up and about
	1/26	0	54 min	0	53 min	Normal	
	2/ 2	0	60 min +	0	60 min +		
	2/14	0	28 min	0	37 min		Slight fever, no other symptoms
	2/15						Home
	4/26						Readmission to hospital, dyspnea, vomiting, jaun- dice, ascites, large liver
	4/27	0	17 min	++++	5 sec		Hemoglobin 75% (Tallquist)
	4/29	+	3½ min	++++	2 sec	Albumin + Casts +	Normal blood chemistry
	5/ 4	++	12 min	++++	1 sec		Marked dyspnea and cyano- sis
	5/ 9						Died, necropsy chronic rheumatic endocarditis, mitral stenosis, cloudy swelling of kidneys
	5 hours postmortem	+++	4 min	++++	1 sec		Test made on cadaver
3 7 years	2/19	0	42 min	0	31 min	Albumin +	Admitted to hospital, dysp- nea, pallor, large liver
	2/23	0	23 min	0	22 min		No dyspnea
	2/28	0	40 min	0	39 min		Scrotal edema
	3/ 9	0	25 min	0	24 min	Normal	
	3/16	0	43 min	0	43 min		Persistent pallor
	3/23	0	29 min	0	21 min		Scrotal edema
	4/ 4	0	38 min	0	37 min	Normal	
	4/14	0	43 min	0	42 min	Normal	Precordial pain
	4/27	0	60 min	0	50 min	Albumin + Casts 0	Normal blood chemistry
	5/ 4	0	39 min	0	17 min		Precordial pain, sacral edema
	5/11	0	40 min	0	29 min	Normal	
	5/15	0	43 min	+	24 min	Albumin +	Face puffy, dyspnea
	5/19	0	27 min	++	27 min	Albumin +	Increased dyspnea
	5/23	0	20 min	+++	4 min	Albumin + Casts +	Rapid and weak pulse
	5/26	0	20 min	+++	2½ min		Scrotal and facial edema
	5/30	+	9 min	+++	1 sec		Marked dyspnea
	5/31						Died, necropsy adhesive pericarditis and rheumatic endocarditis, passive con- gestion of kidneys
	2½ hours postmortem	+	31 min	+++	1 sec		Test made on cadaver

The intradermal salt solution test in the latter class gives results as regards distribution of tissue disturbance comparable to those found by previously mentioned workers in cases of parenchymatous nephritis, scarlet fever and lobar pneumonia. Baker,³ working with cases of scarlet fever and diphtheria, suggested intoxication as the cause of a generalized tissue disturbance resulting in diminished disappearance time. Harrison⁴ offered a similar hypothesis for her results with the test in lobar pneumonia. Anemia of the tissues was advanced by Lazarus-Barlow,⁶ in 1895, as a cause of localized or generalized edema.

CONCLUSIONS

In a group of forty-seven children with rheumatic heart disease, or allied conditions, it was found that

1 The disappearance time of intradermally injected salt solution was normal (above fifty minutes) in well compensated nontoxic cardiac disease, acute rheumatic fever and chorea.

2 In cardiac decompensation with edema, shortening of disappearance time was limited to edematous and preedematous regions and was noted earliest in the dependent parts of the body.

3 Decrease in disappearance time did not precede other clinical signs of impending decompensation with sufficient constancy to make the test of much value in predicting a break in compensation.

4 In certain severely ill patients having cardiac disease without decompensation there was a marked and nearly equal decrease in disappearance time in arm and leg.

5 The intradermal salt solution test was of value in this generalized or toxic group in rendering an unfavorable prognosis.

6 The disappearance time picture characteristic of the toxic group was altered in the direction of that characteristic of the decompensation group, if cardiac decompensation developed.

7 In two patients tested after death, the disappearance time in edematous parts was practically as short as during life, which demonstrated that, under these conditions, circulation of the blood was not necessary in the phenomenon of disappearance of intradermally injected salt solution.

⁶ Lazarus-Barlow, W. S. The Pathology of Edema, *Brit. M. J.* **1**: 634, 691, 1895.

EXCRETION OF PHENOLSULPHONEPHTHALEIN IN OBSTRUCTIVE JAUNDICE [†]

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Whatever the manner in which the normal kidney performs its functions of excreting water, salt, nitrogenous products and foreign dyestuffs like phenolsulphonephthalein, there is not much question that when the kidneys are diseased there is often dissociation of these functions. The importance of the ability of the kidney to excrete phenolsulphonephthalein is particularly emphasized by those cases in which there is a marked diminution of dye excretion while the blood nitrogen figures are normal, or at the upper limit of normal, with the water excretion undiminished. Without discussing the clinical syndromes giving rise to these combinations of expressions of kidney function (not of kidney morphology), it will be assumed that the rate of excretion of phenolsulphonephthalein is one criterion of renal function ¹. And when there is evidence of dysfunction, one method that may aid in estimating diminution of function is the dye excretion.

That there is a relationship between obstructive jaundice and renal disease has been recognized for many years. Certainly significant but as yet not understood, are the changes in kidney morphology in obstructive and toxic jaundice. A recent discussion of the influence of jaundice on the morphology of the kidney is that by Haessler, Rous and Broun ². Quoting Quincke, they emphasize that the distribution of bile pigments is first in the cortex and, as the jaundice persists, there is an increase in the number of pigment granules in the cells of the convoluted tubules and the loops of Henle. Together with many free granules, yellow, green or brown casts then collect in the lumina of the loops. In addition there is cloudy swelling, loss of the brush border, and even necrosis of the tubular epithelium. The glomeruli remain practically unstained.

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1 Rowntree, L G, and Geraghty, T S. An Experimental and Clinical Study of the Functional Activity of the Kidneys by Phenolsulphonephthalein, *J Pharm & Exper Therap* **2** 579, 1910. Eisenbrey, A B. A Study of the Elimination of Phenolsulphonephthalein in Various Experimental Lesions of the Kidney, *J Exper Med* **14** 462, 1911. Beer, Edwin. The Interpretation of Functional Renal Tests with Especial Reference to the Significance of Minimal Excretion of Phthalein and Indigo, *Ann Surg* **64** 435 (Oct) 1916. Mosenthal, H O, and Lewis, D. A Comparative Study of Tests for Renal Function, *J A M A* **67** 933 (Sept) 1916. Sérane, J J. Note sur l'épreuve de l'élimination de la phenolsulphonephthaleine dans ses rapports avec l'azotémie, *Bull et mem Soc med d hôp de Paris* **47** 392 (March 9) 1923.

2 Haessler, H, Rous, P, and Broun, G C. The Renal Elimination of Bilirubin, *J Exper Med* **35** 533 (April) 1922.

Haessler and his associates further discuss their own observations. They point out that the urinary sediments of jaundiced dogs and human beings contain cells of renal origin which are deeply bile stained. This renal pigmentation is believed to be specific evidence of renal injury, and not an expression of sojourn in the bile stained urine. Their statement "After long continued jaundice in man the urinary sediment yields striking indication of the serious condition of the kidneys," is not to be regarded lightly because of the infrequency of diminution of renal function as expressed by our usual tests. In spite of the presence of renal injury, these cases of obstructive jaundice, in the majority of instances, have no evidence of impaired function. Henke and Lubarsch³ describe as the precursors of bile casts coagulated masses in Bowman's capsule. These masses, which are chiefly made up of coagulated protein, are found in the lumina of the tubules, which are dilated and flattened. They state that the epithelium of the proximal convoluted tubules shows marked vacuolization, albuminous degeneration and coagulation necrosis. The blood vessels are normal. There is, however, a group that have nitrogen retention, and in which there is often a terminal uremia⁴. This group will be discussed later. Careful search of the literature has revealed that the excretion of phenolsulphonephthalein has not been reported for cases having normal or abnormal blood nitrogen figures.

The excretion of the dye in obstructive jaundice is important chiefly for these reasons:

- 1 It is a rapid method of estimating a renal function. If the dye excretion were low in a case of obstructive jaundice, extensive operative procedures would be carefully guarded against. A normal dye excretion assures the operator that kidney function is most probably normal, and the dangers of postoperative complications through renal disease are less likely.

- 2 In cases of jaundice complicated by increased or lowered blood nitrogen figures, it may be possible by determination of the dye excretion to present additional evidence for or against the presence of disturbance in renal or hepatic function. The French students of jaundice, for example, have suggested that an increase of blood urea, up to a certain point at least, may be due to hyperfunction of the liver.⁵ Walters and Parham,⁴ in their report from the Mayo Foundation, state that "in a large percentage of cases of obstructive jaundice after the anesthesia was used, the blood urea became double the preoperative

3 Henke, F, and Lubarsch, O. *Handbuch der Speziellen Pathologischen anatomie und histologie* 6 281-285, Berlin, Julius Springer, 1925

4 Walters, W, and Parham, D. *Renal and Hepatic Insufficiency in Obstructive Jaundice*, Surg, Gynec & Obst 35 605-609 (Nov) 1922

5 Cumston, C G. *Icterus Gravis*, New York M J 113 200-201, 1921

value the second or third day after operation. If after operation there is an increase in the cholangitis, or if biliary drainage becomes insufficient, there may be a concomitant increase in nephritis with rising blood urea. These patients sometimes show an alarming picture of uremia and may not recover." A number of typical cases is presented and discussed.

With the intense jaundice of the acute toxic atrophies of the liver, such as acute yellow atrophy⁶ and arsphenamin⁷ poisoning, there have been reported changes in the urea nitrogen of the blood. The low figures, that is, those which are at the lowest limits of normal, are believed to be the result of diminished urea formation by the liver incidental to the destruction of its parenchyma. This is typical of acute yellow atrophy of the liver. In arsphenamin poisoning both low and high figures are found for the urea in the blood, the former probably occurring in the more fulminating liver injuries. In this group of cases of jaundice degenerative lesions are found in the kidneys. The urea nitrogen in the blood may not be taken here as a criterion of renal function because of abnormal urea metabolism, and therefore in this group the determination of the phenolsulphonephthalein excretion may be an important aid in studying renal function.

Before the dye excretion in the presence of jaundice may be evaluated when blood nitrogen changes are present, the influence of jaundice alone on the phenolsulphonephthalein excretion must be known. It is the purpose of this article to report such a control series of cases of jaundice which were uncomplicated by changes in blood nitrogen and which had normal water excretion.

METHOD

The phenolsulphonephthalein was readily determined in the presence of the bile pigments by precipitating the extraneous pigment with an excess of saturated barium hydroxid. This procedure has recently been reported⁸. In urine containing bile pigments, the dye is partially adsorbed during precipitation, the degree of adsorption being dependent on the concentration of pigments and total urine volume. The correction for adsorption is easily determined because the quantity of adsorbed phenolsulphonephthalein in a given specimen of urine whose pigments have been precipitated by barium hydroxid, as far as the accuracy of the test requires, is a constant within the limits of from 0 to 6 mg. (0 to

6 Stadie, W. C., and Van Slyke, D. D. Effect of Acute Yellow Atrophy on Metabolism and on Composition of Liver, *Arch. Int. Med.* **25** 693-704 (June) 1920.

7 Bailey, C. V., and McKay, A. Toxic Jaundice in Patients Under Antisyphilitic Treatment, *Arch. Int. Med.* **25** 628-647 (June) 1920.

8 Abramson, H. A. The Determination of Phenolsulphonephthalein in the Urine in Jaundice, *Arch. Int. Med.* **34** 714-720 (Nov.) 1924.

100 per cent) of the dye For further theoretical considerations the original paper dealing with the method of determination should be consulted The details of the method of determination of the dye are given below

The method devised from the studies on adsorption differs from the routine as follows When there is no correction for adsorption

1 It is preferable to give the dye intravenously but intramuscular injection is almost as suitable

2 The two hour specimen should be divided into two equal parts

3 To one part an excess (urine volume plus 50 c c) of saturated barium hydroxid should be added, and this should be diluted to 500 or 1,000 c c and then filtered A portion of the filtrate should be compared with standards If the 500 c c dilution is used, the reading is direct If 1,000 c c is the dilution, the two hour excretion is the reading times 2 It is, of course, only necessary to catch a few cubic centimeters of the filtrate The dilution to 2 liters aids in colorimetric comparison

4 If the total two hour percentage of excretion of dye is normal or only 5 or 10 per cent below the lower limits of normal, the reading stands as the excretion of the dye and the excretion may be considered normal

When correction for adsorption must be determined

5 If the reading obtained is below normal, it must be determined whether the diminished excretion of the dye is actual or is due to adsorption To the remaining half of the urine, of which the dye content has been determined, 0.25 c c (for 500 c c dilution) or 0.5 c c (for 1,000 c c dilution) of phenolsulphonephthalein should be added With intense jaundice and large urine volume the latter is preferable The percentage of dye in this control should be redetermined

6 The second reading in Paragraph 5 minus the first reading in Paragraph 4 gives the quantity of dye not adsorbed For example, if the first reading (apparent two hour excretion) had been 20 per cent and if to the remaining portions 0.25 c c of the dye had been added, the second reading, granting that none had been lost by adsorption, would be 20 per cent plus 50 per cent (0.25 c c of dye to 500 c c), or 70 per cent If the reading were 50 per cent, instead of 70 per cent, it would be evident that the added dye gave only an additional 50 per cent minus 20 per cent, or 30 per cent of color Hence, three-fifths of the dye added was determined and two-fifths lost by adsorption

7 The final corrected reading of excreted dye is equal to the first reading divided by the fraction not adsorbed, or

$$\frac{20 \text{ per cent}}{3/5} = 20 \text{ per cent} \times 5/3 = 33 \text{ per cent}$$

The Excretion of Phenolsulphonaphthalein in Fifteen Cases of Obstructive Jaundice

Case	Age, Yrs	Clinical Diagnosis	Confirmed Diagnosis	Duration of Jaundice	Urine	Phenol sulphone-phthalein, Two Hour Excretion	Water-Salt Retention	Blood Nitrogen	Blood Cholesterol	Mg per 100 C c	Van den Bergh		Remarks
											Direct	Indirect	
1	40		Multiple neo plasms	5 wk	Bile + + + + +, albumin, trace, hyaline casts, granular casts	40% (intra-venous)	None	Normal	0.254	Pos	12,000		
2	54		Neoplasms with liver metastases	3 wk	Bile + + + + +, otherwise negative	50% (intra-muscular)	None	Normal	0.142	Pos	15,000		
3	23	Catarrhal jaundice		2 wk	Bile + + + + +, otherwise negative	35% (intra-muscular)	None	Normal	Choles-terinemia	Pos	16,600		
4	45	Carcinoma of bile duct		2 wk	Bile + + + + +, otherwise negative	40% (intra-muscular)	None	Normal	0.130	Pos	16,000		
5	24		Hodgkin's disease	5 wk	Bile + + + + +, otherwise negative	60% (intra-muscular)	None	Not ascer-tained	Not ascer-tained	Pos	16,000		
6	36	Infectious jaundice		?	Bile + + + + +, urobilin, negative, albumin, trace hyaline and granular casts	60% (intra-muscular)	None	Normal	0.190	Not done	10,000		Developed secondary nephritis with 0% dye and azotemia
7	50	Neoplasm with common duct obstruction		3 wk	Bile + + + + +, albumin, trace, hyaline and granular casts	45% (intra-muscular)	None	Normal	0.200	Pos	10,000		
8	9		Common duct stone	3 wk	Bile + + + + +, albumin, faint trace, sugar, negative	50% (intra-muscular)	None	Not ascer-tained	Not ascer-tained	Pos	6,000		
9	12		Malignant neo-plasm	4 mo	Bile + + + + +, albumin, trace, granular casts	60% (intra-venous)	None	Normal	0.294	Pos	4,000		
10	31		Adenocarcinoma about ampulla of Vater	6 mo	Bile + + + + +, otherwise negative	40% (intra-muscular)	None	Not ascer-tained	Not ascer-tained	Pos	3,300		
11	70	Neoplasm of duct		5 wk	Bile + + + + +, otherwise negative	50% (intra-muscular)	None	Normal	0.230	Pos	20,000		
12	42		Toxic jaundice (arsphenamin)	5 wk	Bile + + + + +	50% (intra-muscular)	None	Normal	0.100	Pos	30,000		
13	51	Postoperative adhesions?		10 wk	Bile + + + + +, occasional hyaline casts	65% (intra-venous)	None	Normal	0.130	Pos	8,000		Postcholecystectomy
14	15	Catarrhal jaundice?		3 wk	Bile + + + + +, otherwise negative	65% (intra-venous)	None	Normal	0.136	Pos	20,000		Incomplete obstruction
15	72		Carcinoma of pancreas	2 wk?	Bile + + + + +, albumin, trace, hyaline and granular casts	65% (intra-venous)	None	Normal	0.100	Pos	6,000		Hypertension athero-sclerosis

In the event that the colorimetric comparison is not good because the pigment has not all been removed, practically the last traces may be precipitated by making a second dilution using barium hydroxid instead of water as the diluent. The second dilution does not cause much adsorption of dye because the mass of precipitate is usually small. Furthermore, the colorimetric comparison with standards above 30 per cent has been difficult, and the most accurate readings are obtained by comparison with lower values and by then multiplying by the necessary correction factor.

SUMMARY OF RESULTS AND COMMENT

The phenolsulphonephthalein excretion was found to be normal in fifteen cases of obstructive jaundice with a varied etiology. In all of these cases there was no evidence of renal insufficiency. The duration of jaundice was up to six months. Seven cases had periods of intense icterus lasting more than one month. Three of these lasted more than two months. The ages ranged from 12 to 72 years (accompanying table).

It would seem from the morphologic changes in the kidney in jaundice that the degenerative processes are to be found chiefly in the convoluted tubules. In uncomplicated obstructive jaundice, the excretion of phenolsulphonephthalein is normal. This normal excretion of the dye would fit in with the hypothesis that the excretion takes place through the glomeruli of the kidney, since there is apparently no evidence that the severe renal poisons that are present in jaundice influence the structure of the glomeruli.

These prolonged cases of jaundice demonstrate that in uncomplicated obstructive jaundice kidney function as estimated by the foregoing methods is probably unimpaired. What is the influence, then, of obstructive jaundice on diseased kidneys that are functioning normally but whose reserve is near the point at which additional injury may produce diminished function? Are the cases of obstructive jaundice which develop uremia those in which a further slight kidney injury leads to renal dysfunction? And finally the question arises, Is this injury simply due directly to the action of bile pigments and salts on the kidney, or is it due to a disturbance of the total metabolism?

CONCLUSIONS

- 1 The excretion of phenolsulphonephthalein by the kidneys in obstructive jaundice has clinical and physiologic significance.

- 2 In fifteen cases of uncomplicated obstructive jaundice the excretion of phenolsulphonephthalein was found to be normal.

EXPERIMENTAL RENAL INSUFFICIENCY

THE EFFECTS OF HIGH PROTEIN DIET IN THE PRESENCE OF LOW RENAL FUNCTION ON THE KIDNEYS, AORTA AND LIVER, CHANGES IN THE BLOOD PRESSURE AND CONCENTRATION OF BLOOD METABOLITES*

I CONTROLS ON NORMAL DIET

HILDING ANDERSON, M D

DULUTH, MINN

This investigation was undertaken to determine the effect of prolonged renal insufficiency on the blood pressure, and the influence of high or low protein diet on the course of chronic renal disease

The real cause of the progressive development of renal insufficiency in chronic nephritis is not clear. One view is that it is due to repeated infections¹. Day² holds that it is due to a specific infection. Bell³ believes that each new infection occurring in a nephritic patient causes closure of more glomerular capillaries and leaves the patient with a smaller kidney filter than before. Carter, Howe and Mason⁴ suggest as a possibility that progressive damage to the kidneys may result from repeated minimal injury by means of irritating food substances, some of which are known and others as yet unrecognized. Injury to the remaining functioning tissue by high concentration of retained metabolites or by overactivity are other possible causes of the progressive development of insufficiency.

The opinions of different writers vary somewhat concerning the injury to the kidney produced by high concentrations of nonprotein

* From the department of pathology, University of Minnesota Medical School, and St Luke's Hospital, Duluth, Minn

1 O'Hare, J P. Compatibility of Long Life with Low Kidney Function, J A M A **73** 248 (July 26) 1919

2 Day, H B, and Clarke, J K. An Experimental Study on the Origin of Idiopathic Nephritis, Lancet **2** 546 (Sept 11) 1920

3 Bell, E T, and Hartzell, T B. Etiology and Development of Glomerulonephritis, Arch Int Med **29** 768 (June) 1922

4 Carter, H S, Howe, P E, and Mason, H H. Nutrition and Clinical Dietetics, 1917, p 393

nitrogen in the blood. Some maintain that high concentrations are injurious ⁵. Others tend toward the opposite view ⁶.

Methylguanidin, a substance that may be produced from creatinin, is suggested by Boyd ⁷ and Myers ⁸ as a possible cause of uremic symptoms. Major's ⁹ recent work supports this view.

It is well known that a gradual rise of blood pressure is usually observed in chronic glomerulonephritis. This has been attributed by some observers to progressive atrophy of renal tissue ¹⁰. The problem has been attacked experimentally by the removal or destruction of a large part of renal tissue. Pilcher ¹¹ produced renal insufficiency by ligating branches of the renal arteries but obtained no cardiac hypertrophy even after a year. Paszler and Heinke ¹² report a marked left ventricular hypertrophy in seven dogs after surgical reduction of kidney parenchyma. A rise in blood pressure in all seven also is recorded. The average increase was 21.5 mm of mercury. The pressure was measured by means of a cannula in the femoral artery. These experiments have been widely quoted. Janeway ¹³ ligated branches of the renal arteries in nine dogs. Four of the dogs died. Three of those which died and two of those which survived showed a slight rise of blood pressure. The pressure was taken by means of a cuff on the foreleg.

Major ⁹ has recently reported some experiments which show that injections of various guanidin compounds raise the blood pressure in dogs. This is the same substance to which Myers ⁸ and Boyd ⁷ refer as a possible cause of the symptoms of uremia. Major's experiments were carried out under anesthesia with a cannula in the carotid artery.

Aside from the preliminary report of Bell, Clawson and Hartzell ¹⁴ no one has succeeded in producing in animals a disease comparable to

5 Frothingham and Smillie, quoted by Carter, Howe, Mason (Footnote 4) Foster, N. B. Uremia, *J. A. M. A.* **76** 281 (Jan 29) 1921. Vaughn, V. C. The Value and Limitations of a Salt-Free Diet and Restriction of Fluid in Nephritis, *J. A. M. A.* **53** 1789 (Nov 27) 1909. Hewlett, A. W., Gilbert, F. O., and Wickett, A. D. Toxic Effects of Urea on Normal Individuals, *Arch. Int. Med.* **18** 636 (Nov) 1916.

6 McLean, F. C. Mechanism of Urea Retention in Nephritis, *J. Exper. Med.* **26** 181 (Aug) 1917. McLean, Hugh. Treatment of Nephritis, *Lancet* **1** 407 (Feb 28) 1924.

7 Boyd, F. D. Nonprotein Nitrogen of the Blood, Especially in Its Relation to Nephritis and Renal Function, *Edinburgh M. J.* **16** 265 (April) 1916.

8 Myers, V. C. Significance of Metabolism of Creatin and Creatinin with Special Reference to Nephritis, *M. Rec.* **91** 127, 1917.

9 Major, R. H. Relationship Between Certain Products of Metabolism and Arterial Hypertension, *J. A. M. A.* **83** 81 (July 12) 1924.

10 Jawein, G. *Berl. klin. Wchnschr.* **57** 869, 1920.

11 Pilcher. On the Excretion of Nitrogen Subsequent to the Ligation of Successive Branches of the Renal Arteries, *J. Biol. Chem.* **14** 389, 1913.

12 Paszler and Heinke. *Verhandl. d. deutsch. Gesellsch. f. Chir.* **9** 99, 1905.

13 Janeway, T. C. Note on Blood Pressure Changes Following Reduction of Renal Arterial Circulation, *Proc. Soc. Exper. Biol. & Med.* **6** 109, 1908.

14 Bell, E. T., Clawson, B. J., and Hartzell, T. B. Experimental Glomerulonephritis, *Am. J. Path.* **1** 247-258 (May) 1925.

human chronic glomerulonephritis Nephroses are readily produced by uranium, potassium chromate, chloroform and many other substances, but these conditions do not give a chronic renal insufficiency The animals with acute renal insufficiency either die or recover within a short time Even the acute glomerulonephritis produced by Pappenheimer, Hyman and Ziemann¹⁵ by means of bacteria injected directly into the renal artery is transitory

For these reasons various workers have attempted to produce chronic renal insufficiency by removing or destroying a large part of the renal tissue

Pilcher¹¹ and Janeway¹³ ligated portions of the renal blood supply and studied the results The method is not satisfactory because it is not possible to judge with sufficient accuracy the amount of tissue which is incapacitated and because a mass of toxic necrotic material remains

Several workers have removed by operation various proportions of the total kidney tissue¹⁶ All agree that about three fourths may be removed without causing death Karsner found a moderate retention of nitrogen bodies after removal of this amount, but only for a few days Pearce found no change as evidenced by study of the urine

METHODS

It was decided for the purposes of this study to remove a large proportion of the kidney substance surgically When this is being done, the kidney cortex could be reduced any desired amount and a proportion found which would simulate the reduced filter found in chronic nephritis It was realized that the two conditions would not be exactly similar, in chronic nephritis practically all of the glomeruli are at least partially closed,¹⁷ whereas following partial nephrectomy, the small number which remain are entirely normal

The means chosen for watching the course of the changes in the animals were periodic analysis of the blood for creatinin and urea nitrogen, determination of blood pressure, examination of fundus and of the urine, and observations of body weight

When the increase of creatinin was definite, the determination of urea was not always made, especially in the later experiments

15 Pappenheimer, A M, Hyman, H T, and Zeman, F D Acute Glomerular Lesions Following Injections of Bacteria into the Renal Artery, *Proc New York Path Soc* **16** 73, 1916

16 Karsner, H T, Bunker, H A, and Grabfield, G P A Note on the Immediate Effects of Reduction of Kidney Substance, *J Exper Med* **22** 544, 1915 Pearce, R M The Influence of the Reduction of Kidney Substance upon Nitrogenous Metabolism, *J Exper Med* **8** 632, 1908 Bradford, J R Results Following Partial Nephrectomy and the Influence of the Kidney on Metabolism, *J Physiol* **23** 415, 1898

17 Herxheimer Ueber den jetzigen Stand unserer anatomischen Kenntnisse der Nephritis und Nephropathien, *Munchen med Wchnschr* **65** 283, 1918

Animals—The animal used for these experiments was the rabbit. Only healthy animals were used. The blood and urine were analyzed and the blood pressure and weight determined previous to the second operation in each case.

Operative Procedures—The operative procedures followed Bradford's technic rather closely. Two operations with certain exceptions¹⁸ were performed on each animal. A wedge shaped piece was removed from the left kidney at the first operation. After ten days or two weeks the right kidney was removed in toto.

In the first eighteen animals operated on, the average weight of the portions removed from the left kidney was 3.07 Gm. Since all of these animals died of renal insufficiency sooner or later, a smaller portion averaging 2.08 Gm. was removed from the remainder. It is clear that some necrosis occurred in the kidney at the site of the incisions and that any tubules that were cut at any point would undergo atrophy. Therefore, the percentage by weight would indicate only approximately the amount of functioning cortex remaining. If one third of the left kidney were removed, it is obvious that after complete healing less than two thirds would be functioning.

The average weight of the kidneys removed in toto, usually the right, was 9 Gm.¹⁹ The total weight of both kidneys was taken as twice the weight of the right in each case, and was probably only approximately correct. The percentage removed and the percentage remaining were calculated on this basis. The total amount removed varied between 62 and 68 per cent. The amount remaining varied between 32 and 38 per cent.¹⁹ Five rabbits were operated on only once. The left kidney was removed in toto from three (Rabbits 34, 8 and 35) and in part from two (Rabbits 33 and 34).

Blood Analysis—At irregular intervals of ten days or more 5 or 6 cc of blood was drawn by means of a syringe from an ear vein.

The blood analysis was done according to the methods advocated by Folin and Wu.²⁰

In the earlier work comprising about 35 per cent of the experiments all the blood analyses were personally made and most of the solutions were personally prepared by the author. Many of the analyses of the remaining experiments were made by Fred Rytz and Florence Madsen.²¹

18 In the case of diet experiments requiring removal of 15 per cent or 50 per cent of kidney substance, only one operation was performed.

19 Rabbit 15 not included.

20 Folin, Otto, and Wu, Hsien. A System of Blood Analysis, J Biol Chem 38 81 (May) 1919.

21 The urease method for urea determination using whole blood was employed by these two chemists.

Urine Examinations—The urine was collected from the individual animals in a metabolism cage. The volume, specific gravity and presence or absence of albumin were determined and a microscopic examination made on each specimen. When determining the excursions of the variations in specific gravity, the urine was collected several times daily.

Fundus Examination—The fundi were examined from time to time in thirty-two of the rabbits by means of a Welch-Allyn electric ophthalmoscope. Near the end of the study ten of the diet animals were carefully examined by means of a red-free light in order to detect minute blood vessel changes.²²

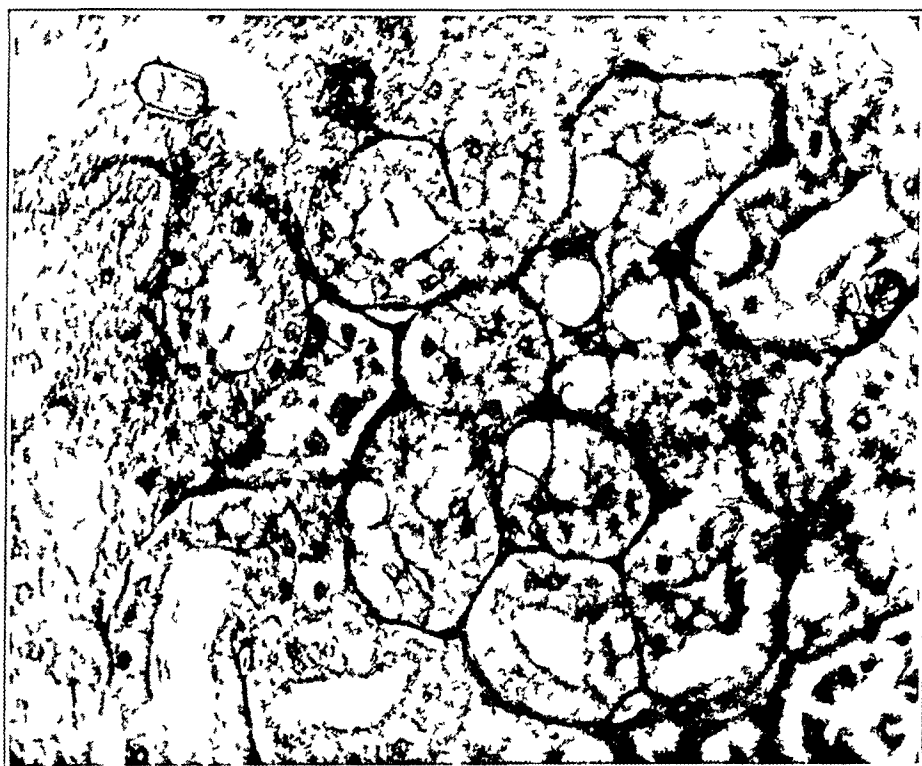


Fig 1 (Experiment 24)—Kidney remnant forty-six days after removal of right kidney, severe hydropic changes

Blood Pressure—The blood pressure was taken in the central artery of the ear by means of an instrument devised for the purpose and described in 1923.²³

This method is, I believe, superior to any other method which I have seen described. It does not cause any discomfort to the animal.

²² Vogt, Alfred. Ueber eine vertikale Streifung, welche an der Vorderfläche der Netzhaut junger Individuen im roten Licht wahrgenommen wird, *Klin Monatsbl d Augenh* 60 47, 1919.

²³ Anderson, Hilding. Demonstration of an Instrument for Taking Repeated Blood Pressures in Rabbits, with Report of Some Experiments, *Proc Soc Exper Biol & Med* 20 295, 1923.

and may be repeated ad libitum over long periods of time. Using a cannula in an artery¹² requires an anesthetic and can be done only once. A cuff on the foreleg is not satisfactory because of the difficulty of palpating the small foot arteries¹³. Cutting out a portion of skin from the leg and holding the animal forcibly is very apt to cause marked variations in the pressure²⁴. In the method used in this study, the variations obtained are only those incidental to the changes in diameter in a peripheral vessel. If heat radiation is carefully controlled, the variations may be largely controlled.

Diets—In the main, only two diets were used, a normal mixed diet and a high protein diet.

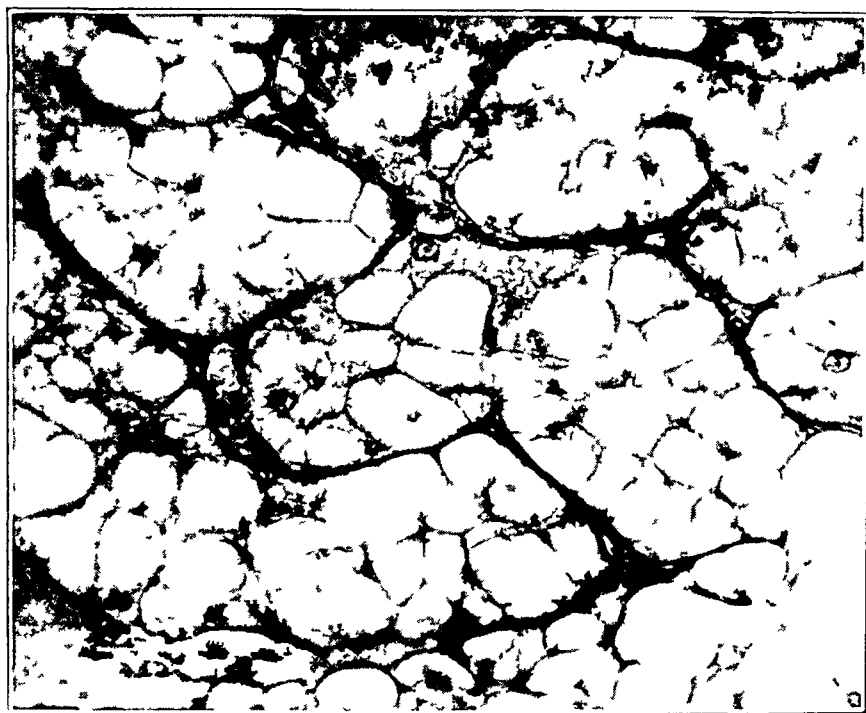


Fig 2 (Experiment 25) —Kidney remnant one hundred five days after removal of right kidney, extreme hydropic degeneration

The normal mixed diet included hay, white bread, carrots, cabbage, celery tops, lettuce, and fresh grass in season. Some of the animals also received oats.

The high protein diet consisted in a bread containing by weight between 55 and 60 per cent of beef²⁵. The other ingredients were

24 Nuzum, F. R., Osburn, Margaret, and Sansum, W. D. The Experimental Production of Hypertension, *Arch Int Med* **25** 492 (April) 1925.

25 This bread may be prepared as follows. The bone, fat and connective tissue are carefully removed from 15 pounds (6.8 Kg.) of roundsteak and the meat passed twice through a fine meat grinder, then 25 parts of meat, 16 parts of graham flour, and 4 parts of ground, dried alfalfa are mixed thoroughly, and 10 teaspoons of baking soda and 3 of salt and water are added to make a stiff dough. This is baked for an hour in a hot oven, or until the bread is moderately hard.

alfalfa and graham flour The alfalfa and graham flour furnished roughage and vitamins This bread contained about 30.5 per cent of protein, 19 per cent of fat, and 50.5 per cent of carbohydrate

When on this diet each rabbit was given a single large leaf of lettuce once weekly

The meat bread was eagerly consumed and the animals appeared to thrive on it

A third diet consisting only of the whites of hard boiled eggs was used in a few instances In the protocols this is referred to as "egg"

Controls—Each step in the study was carefully controlled The effects of the operative procedures were studied in thirty-seven animals on a normal diet before any were given high protein diet The observations made on these thirty-seven included determinations of the effects on the weight, concentration of blood metabolites, and changes in the kidney remnant All of the rabbits in the diet group were studied both before and after operation while still on a normal diet The blood and urine were analyzed, the fundi examined, and the blood pressure and weight studied Each thus became its own individual control In addition, two normal rabbits not operated on (one male and one female from the same litter as some of the others in the diet group) have been included in the diet group and run as parallel experiments similar in every way except the operative procedure A third normal control was started but it did not survive

PROTOCOLS

The experiments on forty-four rabbits are included in this report. The rabbits are divided into three groups as follows (1) those which died before or shortly after the second operation, (2) the operated controls, these survived the second operation but were not given a protein diet, (3) the diet group

For the sake of clearness the results of blood analyses and blood pressure are given in table form or graph when more than a few determinations are recorded The creatinin and urea nitrogen are given in milligrams per hundred cubic centimeters of blood and the blood pressure in millimeters of mercury

GROUP 1

Rabbits 1 to 16 died either before or shortly after the second operation (removal of the right kidney) Most of the valuable data is grouped in Table 1 The blood pressure readings were within normal limits and are omitted

Rabbits 5 to 16 all survived the removal of the wedge from the left kidney At necropsy, two showed hydronephrosis of the remnant In ten the kidney was healed and draining normally Microscopic examination was made in eight Five were normal except along the scar One

showed moderate dilatation and two showed atrophy of the tubules. The atrophy in one of the last was marked and accompanied by scarring in the pelvis. The atrophy in the other was slight.

TABLE 1—*Blood Analyses of Rabbits 1 to 16*

Rabbit	Creatinin	Urea Nitrogen	Rabbit	Creatinin	Urea Nitrogen
1	1.46	13.5	10	1.57 1.9*	24.2 30.8*
2	1.11	24.0	11	1.5*	10.5*
3	1.47	20.0	12	1.6 1.97*	16.6*
4	1.6	11.1	13	1.8*	33.2*
5	1.3 1.37 1.6	27.0 16.2	14		13.0 12.6 27.5* 22.0*
6	1.03	30.0	15	1.4	20.3*
7	1.7	25.1			12.4* 14.0*
8	1.7 1.5*	9.1 9.8*		1.6*	
9	1.9*	18.0*	16	1.65*	

* Rabbits from which a wedge of the left kidney had been removed, in all others both kidneys were intact.

TABLE 2—*Data from Group 2, the Controls Operated On*

Rabbit	Days Survived*	Creatinin	Urea Nitrogen	Kidney Remnant
17	3			Atrophy, dilatation
18	4	3.3 (3)†	125.0 (3)	
19	6			Moderately hydropic
20	10	4.3 (5)	182.0 (5)	
21	13	4.7 (12)	293.0 (12)	Moderately hydropic
22	14	3.1 (3) to 7.0 (14)	103.6 (3) to 362.6 (14)	Atrophy, dilatation
23	21	3.1 (8)	44.8 (8)	Marked atrophy
24	46	2.4 (14) to 4.0 (45)	23.5 (14) to 150.0 (45)	Markedly hydropic
25	107	2.1 (6) to 6.0 (106)	49.0 (6) to 275.0 (106)	Extremely hydropic
26	117	1.7 (6) to 5.1 (115)	49.0 (6) to 216.4 (115)	Hydronephrosis
27	119	1.7 (14) to 3.8 (82)	44.0 (14) to 156.0 (114)	Marked atrophy
28	167	2.2 (66)	27.1 (48)	Atrophy, dilatation (calculus)

* The number of days the animal survived the second operation.

† The numbers in parentheses indicate the day following the second operation when the analysis was made (Figs 1 to 5).

GROUP 2

This group includes those animals which survived both operations and were available for further study. This group serves as a series of operated controls for the diet group operated on (discussed in Part II of this article) and includes Rabbits 17 to 28. Table 2 contains the essential data.

NORMAL VALUES

Analyses were made on twenty-seven samples of normal blood taken from twenty-three rabbits not operated on eating a normal diet²⁶ and on twenty-eight samples taken from twenty-four rabbits that had been through the first operation (from 10 to 20 per cent of kidney substance removed)

The normal range of blood pressure was rather wide. Most readings lay between 70 and 86, although readings as low as 60 and as high as 90 were not uncommon. There was considerable variation between individuals. Usually any one individual yielded fairly consistent readings.

The specific gravity of the urine varied from 1.006 to 1.036 in the animals that were not operated on.

PROGRESS OF THE CONTROLS IN WHICH OPERATION WAS DONE

Rabbits 17 to 28 survived the second operation for a time varying from three to 167 days. None of these were given the high protein diet at any time but serve as a control series for the diet group.

Blood Metabolites—The blood chemistry changes were characterized in general by a progressive accumulation of metabolites. There was a slight rise in the concentration of creatinin after the removal of the wedge from the left kidney. This was apparent only after averaging

TABLE 3—*Analysis of Normal Blood*

	Number of Analyses	Average per 100 Cc	High Figure	Low Figure
Creatinin	24	1.48 mg	1.9 mg	1.03 mg
Urea nitrogen	20	17.79 mg	30.0 mg	9.1 mg
Results of Analysis of Blood after First Operation				
Creatinin	23	1.67 mg	2.1 mg	1.3 mg
Urea nitrogen	22	17.80 mg	33.2 mg	9.1 mg

many cases. Beginning almost immediately after the removal of the right kidney there was a definite gradual increase in the concentration of creatinin and urea nitrogen which was progressive until death (Figs. 3, 4 and 5). Karsner¹⁶ found no retention until more than three-fourths had been removed. The rapidity of this increase in concentration bore an inverse ratio to the length of time the animals survived. Those in which the accumulation was slowed lived long, and those in which it was rapid died early.

All those which showed a progressive accumulation until death had apparently been deprived of too much kidney substance. Rabbits 17 to 22 lived fourteen days or less. The average weight of the wedge

²⁶ Hammett, F. S. Studies of Variations in the Chemical Composition of Human Blood, *J. Biol. Chem.* **41**: 599 (April) 1920.

removed from the left kidney in these was 3.15 Gm. Rabbits 23 to 28 lived from twenty-one to 167 days. The average weight of the wedge was 2.12 Gm. The rate of accumulation was much slower in these.

The health of the animals continued apparently good until a decided retention had developed. When the concentration of urea rose as high as from 80 to 100 mg and the creatinin to 3 or 3.5 mg, the animals began to lose weight and to become less lively. Weakness began to be apparent and the animals failed to eat well. Finally, as the concentration rose still higher a day or two before death, they quit eating entirely. The more severe symptoms usually developed only a few days before death. No convulsions were observed in any.

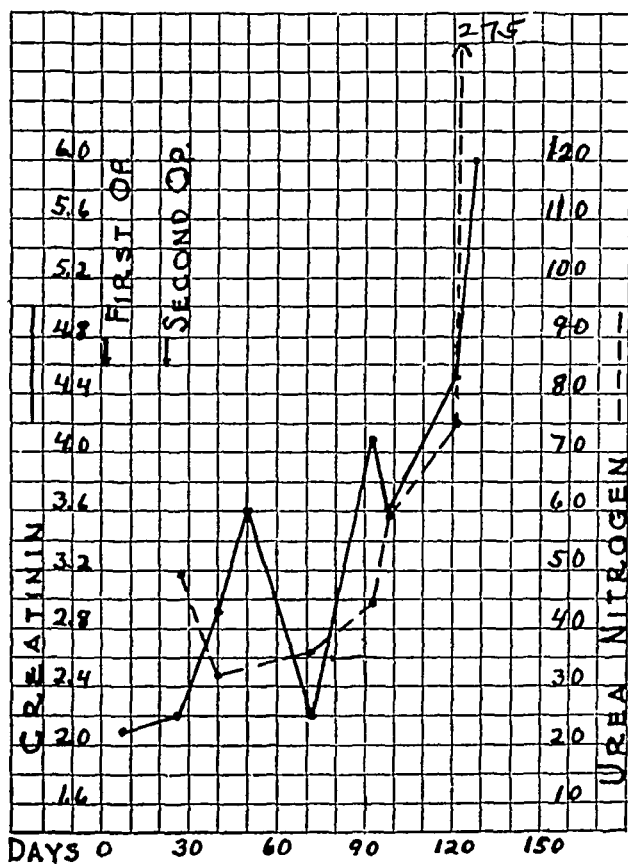


Fig. 3—Findings in Experiment 25

Pregnancy seemed to have an injurious effect on Rabbit 24 (Fig. 1). Two weeks after operation it showed only a small accumulation. About six weeks after operation it delivered young. Four days after delivery it died with a high urea, estimated at 400 mg.

Rabbits 26 and 28 showed a progressive rise in creatinin values and then a drop to normal. A second accumulation then began which progressed until death. At necropsy a calculus was found in each. These lived 117 and 167 days, respectively.

Rabbit 27 lived 119 days. The rise in creatinin was gradual but steady. There was no tendency toward a return to normal. At necropsy, the remnant showed signs of progressive closure of the tubules.

Urine Changes—The urine changes were consistent with a simple reduction in the kidney filter.

The specific gravity tended strongly toward fixation (Table 4). This was greatest in those which suffered the highest degrees of insufficiency and least in those which were most nearly normal. Fixation occurred in most cases between 1.012 and 1.018. Rabbit 28 best illus-

TABLE 4—*Specific Gravity of the Urine in Relation to the Operative Procedures*

Rabbit	Day of Experiment	Preoperative	After First Operation	After Second Operation
7	215 to 221		1.008 to 1.020	
14	240 to 245		1.016 to 1.022	
15	28 to 35 185 to 189	1.016 to 1.025	1.016 to 1.021	
16	8 to 11 11 to 14 64 to 67	1.018 to 1.032	1.028 to 1.033 1.012 to 1.028	
27	64 to 68 115 to 121			1.011 to 1.017 1.014 to 1.016
28	37 to 39 52 to 57 73 to 74 74 to 80 93 to 95 119 to 123 171 to 174 176 to 178	1.015 to 1.030	1.015 to 1.027 1.025 to 1.031	1.017 to 1.024 1.020 to 1.024 1.015 to 1.018 1.010 to 1.014 1.008 to 1.014
29	212 to 216 233 to 235		1.012 to 1.032	1.012 to 1.018
38	51 to 56 143 to 149 412 to 416			1.008 to 1.016 1.012 to 1.020 1.008 to 1.020
39	12 to 17 25 to 28		1.010 to 1.030	1.016 to 1.018 1.013 to 1.020
42	31 to 33			
43	26 to 28 33 to 35		1.012 to 1.024	1.010 to 1.012
44	200 to 206 258 to 262 263 to 266 436 to 440		1.012 to 1.026	1.022 to 1.031 1.014 to 1.022 1.006 to 1.020

trates the progression of fixation and loss of power to concentrate. Beginning with the concentration 1.031, it gradually lost concentration power until 1.014 was the upper limit.

The volume varied so greatly in both those operated on and those not operated on that no significant figures were obtained.

Albumin was found only occasionally and then only in traces unless complications had intervened.

Blood Pressure—The blood pressure findings were quite unexpected. From clinical experience and from what little experimental

work had been done it was gathered that the blood pressure would surely rise proportionately to the reduction of the kidney substance ²⁷

No hypertension resulted even in the cases of high grade insufficiency (Fig 5) ²⁸ The blood pressure was observed on thirty-three rabbits (including some which later fell into the diet group) over the period of time which they were under observation No significant rise was observed in any as a result of or accompanying the reduction of kidney substance Occasionally there seemed to be a slight postopera-

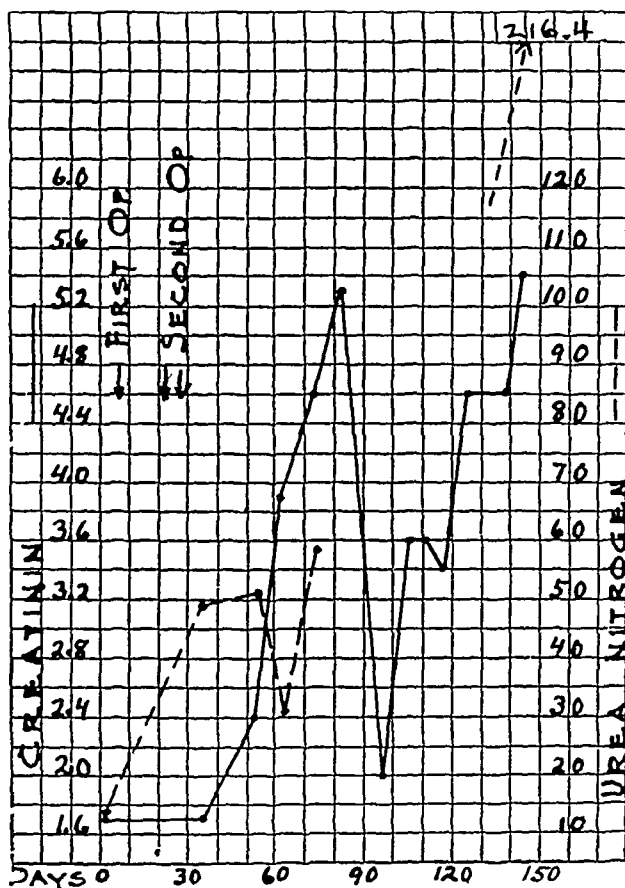


Fig 4—Findings in Experiment 26

tive rise, as in Rabbits 15 and 16, but this was usually small and within normal limits and could often be accounted for by fear or an insufficient number of preoperative determinations These rises were no greater than the variations frequently observed in normal animals Moreover,

²⁷ Jawein (Footnote 10) Heinike and Paszler (Footnote 12) Janeway (Footnote 13) Pilcher (Footnote 11) Cash, J R Study of Blood Pressure Following Reduction of Renal Substance, Bull Johns Hopkins Hosp **35** 168 (June) 1924

²⁸ A preliminary report on some of these animals has been made by Anderson, Hilding The Relation of Blood Pressure to the Amount of Renal Tissue, J Exper Med **39** 707 (May) 1924

just as great a postoperative fall was occasionally found (Rabbit 40, discussed in Part II of this article)

Of the thirty-three on which the blood pressure was observed the kidney substance had been reduced by approximately 65 per cent in twelve, and by from 12 to 50 per cent in eight. The remainder were normal at the time of the blood pressure determinations. Renal insufficiency obtained in most of the twelve and a number died as a result of insufficiency.

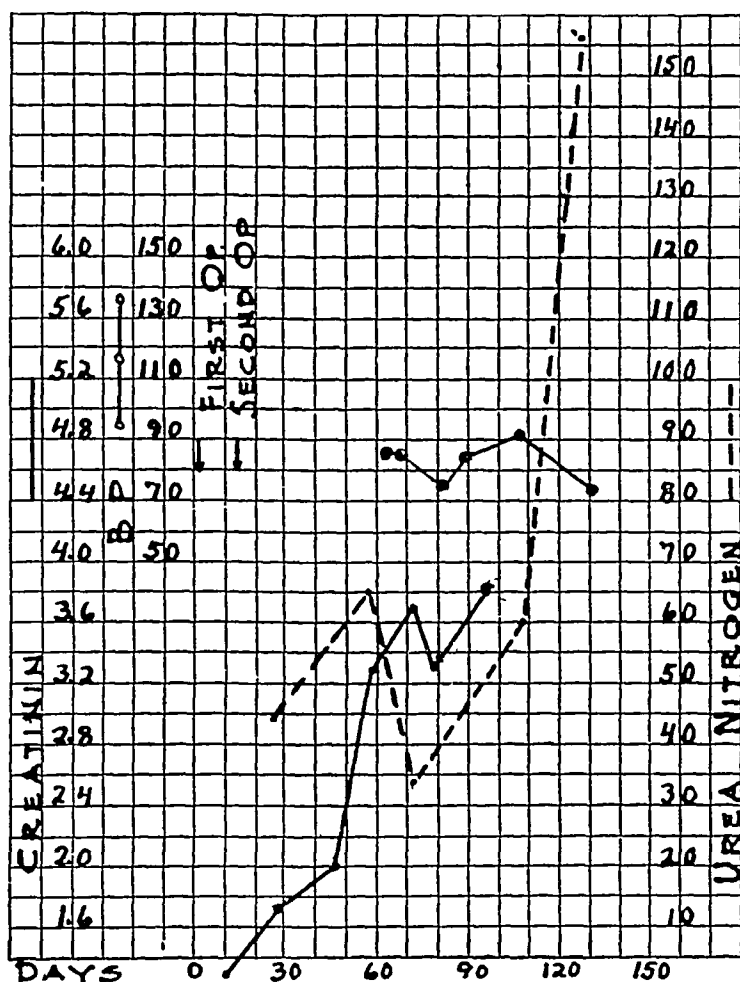


Fig 5—Findings in Experiment 27

No renal hypertension was observed in any. Yet in special experiments with epinephrin, guanidin and intravenous saline increased blood pressure was obtained. This showed that the failure to obtain hypertension was not due to the method of determining the pressure.

Fundi—The fundi were examined from time to time in a few of this group. A search was made in each case for signs of arteriosclerosis and albuminuric retinitis. No changes were observed. They all appeared essentially normal at all times.

Weight—The weight maintained a normal course in each operated rabbit after recovery from the operations unless death intervened from some cause. A few days before death there was a fall in weight.

All of the rabbits were watched for convulsions and signs of edema. None were observed at any time. This is consistent with clinical findings. Patients may die from renal insufficiency and develop no edema. Many have no convulsions.²⁹

NECROPSY FINDINGS IN CONTROLS THAT WERE OPERATED ON (TABLE 5)

Changes in the Kidney Remnant—The gross change in the kidney remnant, unless complications were present, was a simple hypertrophy. If the left kidney had been removed or destroyed the right hypertrophied. This hypertrophy reached the high degree of 22.5 Gm. in the case of Rabbit 15 which lived 168 days after the destruction of the left kidney. The remnant of the left kidney, which had been operated on, after removal of the right hypertrophied to such an extent that it sometimes weighed as much or more than the right (Rabbits 26 and 27).

TABLE 5—Summary of Operative Procedures and Necropsies in Twelve Controls That Were Operated On

Rabbit	Days Survived After Second Operation	Weight of Piece of Left Kidney Excised, Gm.	Weight of Right Kidney, Gm.	Percentage of Kidney Substance Remaining	Weight of Remnant of Left Kidney Gm.	Microscopic Findings in Remnant
17	3	3.18	10.0	38.0	5.5	Atrophy, dilatation
18	4	3.32	10.0	33.4		
19	6	3.1	10.1	34.7		Moderately hydropic
20	10	3.7	10.0	31.5	7.2	Postmortem autolysis
21	13	3.0	8.4	32.1	4.2	Moderately hydropic
22	14	3.6	10.1	32.2		Atrophy, dilatation
23	21	1.90	8.5	38.5	5.6	Marked atrophy
24	46	1.9	7.5	37.3	7.0	Markedly hydropic
25	105	2.25	7.25	34.5	6.8	Extremely hydropic
26	116	3.0	10.4	35.7	10.3	Hydronephrosis (calculus)
27	119	1.9	7.9	37.3	9.7	Marked atrophy
28	168	1.8	7.9	38.6	7.0	Atrophy, dilatation (calculus)

Microscopically the remnant in all of this group showed marked pathologic changes. This was evidenced by varying degrees of hydropic change in the tubular epithelium or by atrophy of the tubules and glomeruli with or without dilatation.

The hydropic change was diffuse and differed in this respect from the small patches of hydropic degeneration found frequently in otherwise normal kidneys. In this group four showed hydropic change. These were Rabbits 19, 21, 24 and 25. The severity increased with length of life (Figs 1 and 2), being most severe in Rabbit 25, which lived 107 days.

29 Foster (Footnote 5, second reference)

This hydropic change was not a result of the operation on the kidney. It did not occur in the animals operated on which showed no retention of metabolites or died before the second operation (Rabbits 7, 9, 14, 11, 12 and 33).

Two possibilities present themselves as the cause of this tubular injury: first, the toxic effect of retained urinary bodies, second, an exhaustion phenomenon following hyperactivity on the part of the renal epithelium, due to the greatly increased demand made on it.

In any case, this hydropic degeneration seems to represent the pathologic changes in the kidney remnant when the rabbits died of renal insufficiency uncomplicated by other local factors.

Complications resulted in some cases following the operation on the left kidney. Renal calculi occurred in four (Rabbits 26, 28, 39 and 40). Three of the four showed gross or microscopic signs of obstruction.

Obstruction occurred a number of times from other causes. In Rabbit 17 a necrotic mass of material was found in the pelvis. Rabbit 5 showed an old clot in the pelvis which extended into the ureter. In Rabbit 13 the pedicle had become twisted. All three showed gross or microscopic evidence of marked obstruction.

Rabbits 22, 23, 27 and 28 showed marked atrophy of all structures with varying degrees of tubular dilatation. They all gave the typical microscopic appearance of hydronephrosis but grossly there was no dilatation and the drainage appeared good. It was finally determined that removal of a portion of the single pyramid and progressive scarring about the excretory ducts brought about this condition (Rabbits 15 and 23).

Aorta—No pathologic changes of any kind were observed in the aorta in any of the rabbits that had been fed a normal diet only. This shows that the changes observed in the high protein animals were not due to low renal function. Even those which died following a protracted renal insufficiency did not show arteriosclerosis.

SUMMARY OF CONTROLS IN WHICH OPERATION WAS PERFORMED

A condition of low renal function simulating the reduced kidney filter of chronic renal disease was produced in rabbits by removing portions of the kidneys by surgical means. Between 60 and 70 per cent of the total kidney substance was destroyed in this way.

Following the operative procedures in which over 60 per cent of kidney substance was destroyed, there was a retention of creatinin and urea nitrogen in the blood. This became progressively greater until death in Group 2.

There was no increase in blood pressure following the reduction of kidney substance, even in those which died from a slowly progressive renal insufficiency

All in the second group died of renal insufficiency The kidney remnant uniformly showed hypertrophy Only four showed no gross or microscopic signs of obstruction These four all showed diffuse hydropic change, which was probably due to overactivity

The aorta appeared normal at necropsy The liver in some exhibited fatty metamorphosis

This article is in two parts, Part II will deal with partially nephrectomized rabbits on a high protein diet

EXPERIMENTAL RENAL INSUFFICIENCY

THE EFFECTS OF HIGH PROTEIN DIET IN THE PRESENCE OF LOW RENAL FUNCTION ON THE KIDNEYS, AORTA AND LIVER, CHANGES IN THE BLOOD PRESSURE AND CONCENTRATION OF BLOOD METABOLITES *

II PROTEIN DIET EXPERIMENTS

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It has long been held, apparently largely on theoretical considerations, that a chronic nephritis with nitrogen retention is benefited by a low protein diet. Hugh McLean¹ explains that the theory originated in a misconception of protein metabolism. He states (1924) that there is no proof that protein food is in any way injurious to the kidneys. He admits that a high concentration of nitrogen metabolites may be injurious and that in advanced cases of nephritis in which this condition is present it may be of value to limit the proteins.

Nevertheless, the therapy of protein limitation has found widespread acceptance in the treatment of Bright's disease and is extensively used.² Newburgh and Clarkson³ report experimental studies in the feeding of a high protein diet to rabbits. They feel that they have produced a very definite renal injury by feeding a diet containing 36 per cent protein over a period of months. O'Hare,⁴ on the other hand, seems to feel that repeated infections have more to do with injury to the kidneys than excessive protein in the diet.

A number of observers⁵ have shown conclusively that the concentration of nonprotein nitrogen in the blood of nephritic patients is increased

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1 McLean, Hugh. Treatment of Nephritis, *Lancet* **1** 407 (Feb 23) 1924.

2 Janeway, T. C. Management of Patients with Chronic Renal Disease, *Am J M Sc* **151** 157 (Feb) 1916. Anders, J. M. Treatment of Chronic Bright's Disease, *M Rec* **92** 311 (Aug 25) 1917. Arnold, H. D. Importance of Low Protein Diet in Chronic Nephritis, *J A M A* **55** 2193 (Dec 24) 1910. Carter, H. S., Howe, P. E., and Mason, H. H. Nutrition and Clinical Dietetics, 1917, p. 393. Motzfeldt, K. Dietetic Treatment of Renal Insufficiency, *Acta med Scandinav* **53** 611, 1920. Foster, N. B., and Davis, Helen B. Effect of Water Intake on Nitrogen Retention in Nephritis, *Am J M Sc* **151** 49 (Jan) 1916.

3 Newburgh, L. H., and Clarkson, S. Renal Injury Produced in Rabbits by Diets Containing Meat, *Arch Int Med* **32** 850 (Dec) 1923.

4 O'Hare, J. P. Compatibility of Long Life with Low Kidney Function, *J A M A* **73** 248 (July 26) 1919.

5 Chace, A. F., and Rose, A. P. Dietetic Treatment of Nephritis, *J A M A* **69** 440 (Aug 11) 1917. Folin, Otto, Denis, W., and Seymour, M. The Nonprotein Nitrogen Constituents of the Blood in Chronic Vascular Nephritis as Influenced by the Level of Protein Metabolism, *Arch Int Med* **13** 224 (Feb) 1914. McLean, F. C. Mechanism of Urea Retention in Nephritis, *J Exper Med* **26** 181 (Aug) 1917. Hewlett, A. W., Gilbert, Q. O., and Wickett, A. D. Toxic Effects of Urea on Normal Individuals, *Arch Int Med* **18** 636 (Nov) 1916.

or diminished markedly by corresponding changes in the quantity of protein in the diet. But it does not necessarily follow that these changes in the blood influence the general condition of the patient or the course of the disease. McLean⁶ quotes data from a case of nephritis in which the blood urea was made to vary from 26 to 254 mg per hundred cubic centimeters without changing either the subjective or the objective symptoms of the patient. Folin, Denis and Seymour,⁷ on the other hand, noted headache, nausea, lassitude and gastro-intestinal disturbances in patients to whom they fed a high protein diet. They did not note any extensive increase in the blood urea. Opie and Alford⁸ found experimentally that potassium chromate and uranium nitrate were more potent in producing nephritis in animals that were fed on a meat diet.

GROUP 3

The sixteen rabbits in Group 3 were fed a high protein diet (30.5 per cent protein) over varying periods of time. Thirteen were partially nephrectomized. They all recovered and returned to normal values of blood creatinin and urea before receiving the high protein diet.

They were divided into four subgroups. Subgroup A includes three normal rabbits. Subgroups B, C and D had been deprived of 12 per cent, 50 per cent and 65 per cent of kidney substance, respectively. Subgroups B and C include two rabbits each and Subgroup D includes nine.

PROTOCOLS

For the sake of clearness, the data in the protocols pertaining to the following points is given in table form or chart if many observations are recorded, namely, diet, creatinin and urea nitrogen concentrations, blood pressure and weight. In the diet column, the word protein is used to indicate the time when the animal was placed on the high protein diet, and the word normal to indicate the time when it was replaced on a normal diet.

The necropsies were made complete as a routine matter and included examination of the following: peritoneal cavity, amount of fat present, pleural cavities, lungs, heart, spleen, liver, stomach and intestines, kidneys, suprarenals, aorta and, in the female, tubes, ovaries and uterus. A microscopic examination was made of the lungs, heart, spleen, liver, intestine, kidneys, suprarenal, aorta, voluntary muscle and, in the female, of the tubes, ovaries and uterus. Only the positive or significant findings are given.

6 McLean (Footnote 5, third reference)

7 Folin, Denis and Seymour (Footnote 5, second reference)

8 Opie, E. L., and Alford, L. B. Influence of Diet upon Necrosis Caused by Hepatic and Renal Poisons, *J. Exper. Med.* **21** 1, 1915

Subgroup A Controls Not Operated On—Two of these are shown in Figures 1 and 2. There was no increase of creatinin or urea nitrogen. The blood pressure remained normal. The animals ate the meat bread well and increased in weight. In Rabbit 30 there was moderate sclerosis of the aorta and a marked hydropic change in the liver. The kidneys were enlarged, together weighing 23 Gm. In Rabbit 31 there was a marked sclerosis of the aorta with extensive atheroma and calcification and saccular dilatation (Fig. 3). The kidneys together weighed 28.4 Gm. There was a marked hydropic change in the liver.

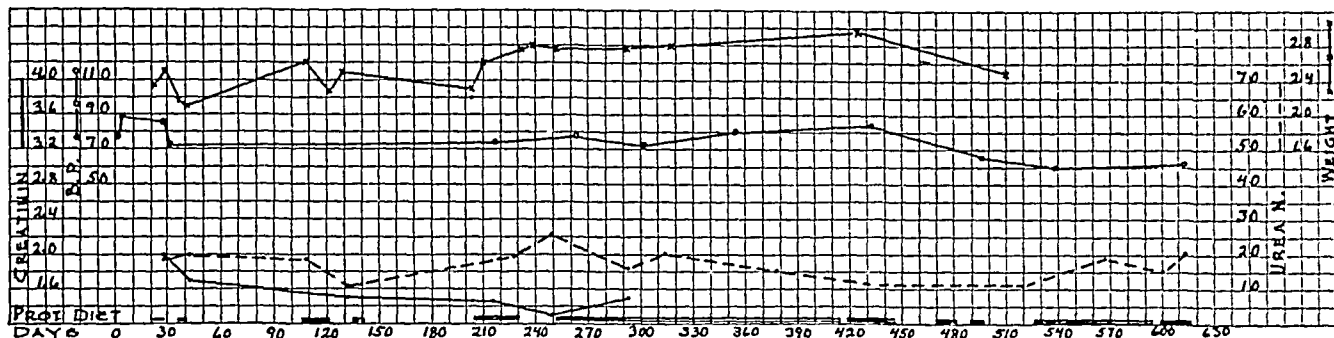


Fig. 1—Findings in Experiment 30



Fig. 2—Findings in Experiment 31

Subgroup B—The kidney substance in these two rabbits (Rabbits 32 and 33) was reduced about 12 per cent. Each was subsequently kept on the protein diet fifty-two days. The creatinin did not increase, but there was a slight increase of urea nitrogen (35 mg) in Rabbit 32. The blood pressure remained normal. The aorta of Rabbit 33 was normal, but there was moderate atheroma in Rabbit 32. Marked hydropic changes in the liver were noted in both animals.

Subgroup C—These two animals (Rabbits 34 and 35) were deprived of about 50 per cent of the renal tissue by removal of the entire left kidney. Each was subsequently kept on the protein diet eighty-seven days. When killed at the close of the experiment both

were very fat There were no changes in the retinal vessels There was definite hypertrophy of the remaining kidney (14.7 and 12.3 Gm.) A slight atheroma of the aorta was found in Rabbit 34 and moderate atheroma in Rabbit 35 The liver showed moderate hydropic change in Rabbit 34 and a fatty metamorphosis in Rabbit 35 The blood pressure remained normal A moderate rise in creatinin and urea nitrogen occurred (Table 1)

Subgroup D—This group includes those rabbits which were deprived of 65 per cent of kidney substance and were fed a high protein diet

TABLE 1—*Analysis of Rabbit 35*

Day of Experiment	Diet	Creatinin	Urea Nitrogen
1 (first operation)			
6			
7			
22	Protein	1.8	17.5
35		2.5	40.6
63		1.7	35.2
92	Normal Protein		
95			
96		1.7	43.4
109	Normal	2.4	37.1
113			

TABLE 2—*Analysis of Rabbit 36*

Day of Experiment	Diet	Creatinin	Urea Nitrogen	Blood Pressure	Weight, Kg.
1				75	
35				84	
193 (first operation)					
214		2.0			
216			20.1		
219				78	
228 (second operation)					
249				90	
254			26.1		
273		1.8			
280				87	
281	Egg				
283					2.27
285					1.93
286	Normal		27.1		

EXPERIMENT 36 (Female, Table 2)—The experiments were begun July 5, 1922, death occurred April 23, 1923, the two hundred and ninety-second day

Day 1, the animal was three-fourths grown

Day 193, the left kidney was removed, the weight was 7.8 Gm., microscopically, it was normal

Days 212 to 216, the specific gravity of eight specimens varied from 1.012 to 1.032

Day 216, albumin was absent

Day 228, the right kidney was operated on and between one third and one half of the cortex infarcted

Days 231 to 235, the specific gravity in three specimens was from 1.012 to 1.018

Day 234, albumin was absent

Day 281 the animal was placed on an egg and bean diet

Day 286 the animal was taken off the egg and bean diet, she had eaten practically nothing during the five days

Day 290, the animal delivered young

Day 292, the animal died The total number of days on the high protein diet was five, she survived the operation on the right kidney sixty-four days

At necropsy the right kidney weighed 11.9 Gm Three large infarcts were found in the cortex These areas were atrophied The living cortex was rather soft, the ureter and pelvis appeared normal There were no signs of obstruction

Microscopic examination of the right kidney showed nothing abnormal in the functioning cortex The infarcted areas were completely atrophied

Hypertrophy of the right kidney was the abnormal finding

EXPERIMENT 37 (Table 3) —Experiments were begun May 5, 1923, death occurred Nov 15, 1923, the one hundred and ninety-fourth day

Day 1, three areas totaling 50 per cent of the left kidney cortex were infarcted

Day 34, the right kidney was removed, the weight was 8.2 Gm, microscopically, it was normal

Day 130, the creatinin was 17 mg

Day 194, the animal died, having survived the removal of the right kidney 160 days The total number of days on a high protein diet was twenty-three The carcass was lost

TABLE 3—*Analysis of Rabbit 37*

Day of Experiment	Diet	Urea Nitrogen	Blood Pressure	Weight, kg
1 (first operation)				
5		10.75		
34 (second operation)				
40			88	
90			70	
105	Protein			
107				2.04
113				2.10
117		36.15		
119	Normal			
130		21.7		
133	Protein			
140	Normal			
151			71	

EXPERIMENT 38 (Male, Fig 4) —The experiments were begun March 18, 1922, death occurred July 1, 1923, the four hundred and sixty-ninth day

Day 5, 2 Gm of the left kidney was removed, microscopically, this was normal

Day 20, the right kidney was removed, the weight was 7.3 Gm, microscopically, it was normal

Days 49, 50 and 52, albumin was absent (Table 4, Paper I)

Day 60, the fundi were normal

Day 142, the fundi were normal

Days 142, 143 and 146, albumin was absent

Day 268, the fundi were negative

Day 401, phenolsulphonaphthalein elimination was 60 per cent

Days 411 to 414, the animal was on egg diet

Day 411, albumin was absent

Day 414, a trace of albumin was present The sediment showed occasional hyaline casts The animal ate practically none of the egg offered it during these days

Day 414, the animal was given a diet of meat bread (see methods), it ate small amounts of this

Day 415, no urine was excreted in twenty-four hours

Day 416, the first bowel movement was passed since the animal was placed on the egg diet on Day 411 The urine measured 147 cc, specific gravity was 1.025, there was a trace of albumin and a few casts were present

Day 417, the animal was replaced on a normal diet The animal had eaten almost nothing since Day 410

Day 430, phenolsulphonephthalein elimination was 45 per cent

Day 469, the animal died, 449 days after the removal of the right kidney. The total number of days on the high protein diet was seventeen

EXPERIMENT 39 (Male, Fig 5) —The experiments were begun May 3, 1923, death occurred March 15, 1924, the three hundred and eighteenth day

Day 1, the animal was about three months old and not fully grown

Day 3, the left kidney was operated on, 50 per cent of the cortex was infarcted

Days 13 and 14, albumin was absent, but on Day 17 after the operation a trace was found (Table 4, Paper I)

Day 17, the right kidney was removed, the weight was 117 Gm, microscopically, it was normal

Day 271, the specific gravity of the urine was 1.015, albumin was +, the sediment showed occasional pus cells

Day 272, the specific gravity of the urine was 1.025, albumin was absent

Day 303, the right forefoot was lame, he refused to bear weight on it



Fig 3—(Experiment 31) —Aorta of control not operated on after 324 days on high protein diet, marked atheromatous change in intima

Day 318, the animal was sick and emaciated, the fur was soiled, and the left eye was suppurating in an old injury to the lid. Calcium totaled 12 mg per hundred cubic millimeters of blood. He was killed by a blow on the head, 301 days after the removal of the right kidney. The total number of days on the high protein diet was 128

At necropsy the left kidney weighed 115 Gm. The cortex was swollen, cloudy and wet, and there was a stone in the pelvis. The aortic ring was hard and calcified, otherwise apparently normal. The entire aorta was dilated and markedly sclerosed throughout its length. The walls were calcified and so stiff that they fractured when handled. There were many transverse, yellow rings and a few yellow plaques present. There was no marked thickening of the intima.

Microscopically the glomeruli and tubules of the kidney appeared hypertrophied, there were a few small areas of hydropic change.

Marked arteriosclerosis, renal calculus and renal hypertrophy were the abnormal findings.

EXPERIMENT 40 (Female, Fig 6) —The experiments were begun Sept 21, 1923, death occurred Sept 11, 1924, the three hundred and fifty-seventh day

Day 2, 23 Gm of the left kidney was removed, microscopically, this was normal

Day 9, the right kidney was removed, the weight was 83 Gm, microscopically, it was normal

Day 107, the animal was pregnant

Day 126, the animal was pregnant

Day 128, she delivered young The young died quickly

Day 143, albumin was absent

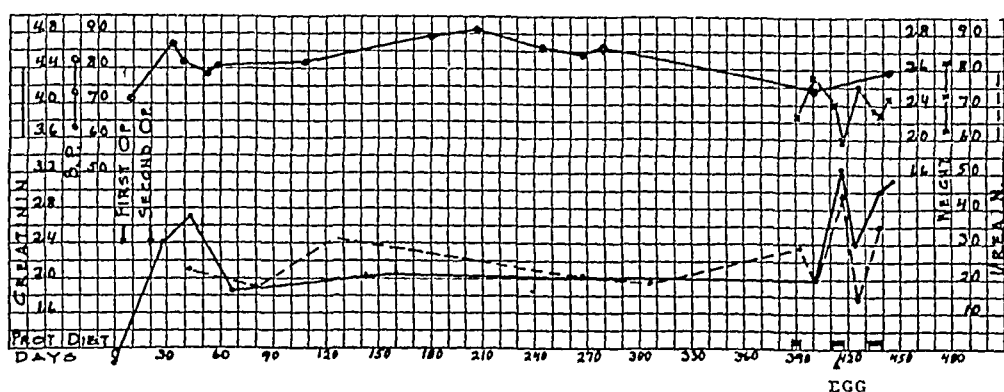


Fig 4—Findings in Experiment 38

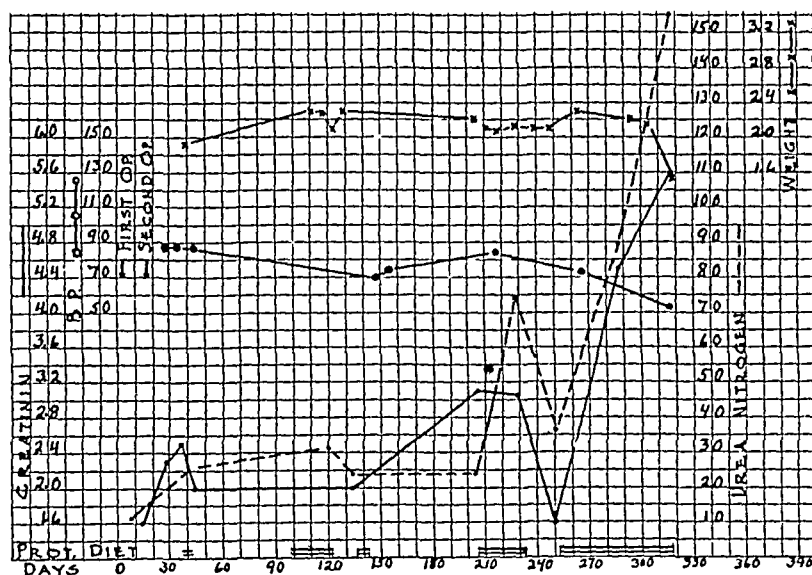


Fig 5—Findings in Experiment 39

Day 179, calcium was 155 mg per hundred cubic centimeters of blood

Day 180, the specific gravity of the urine was 1025, albumin was +, many red blood cells were present in the urine

Day 331, the animal delivered young She was placed in an individual cage and the young were carefully guarded, but they all died quickly

Day 356, she appeared sick and refused to eat

Day 357, she was sick and thin At 9 15 p m she was given 01 Gm of methyl guanidine sulphate intravenously, at 11 p m she died in mild convulsions The animal survived the removal of the right kidney 348 days The total number of days on the high protein diet was 238

At necropsy the left kidney was found to be adherent by scar tissue to the abdominal wall, the cut surface was moist with yellowish striations, the pelvis was somewhat dilated, a stone was found in the beginning of the ureter

The aortic leaflets of the heart were thickened and the ring was thickened and hardened, otherwise the heart was normal. The aorta contained many atheromatous plaques throughout its entire length

Microscopically, there were occasional glomeruli in the kidney with fairly normal tubules but the great majority had disappeared entirely. The liver showed no degeneration

The abnormal findings were renal calculus and pyelonephritis

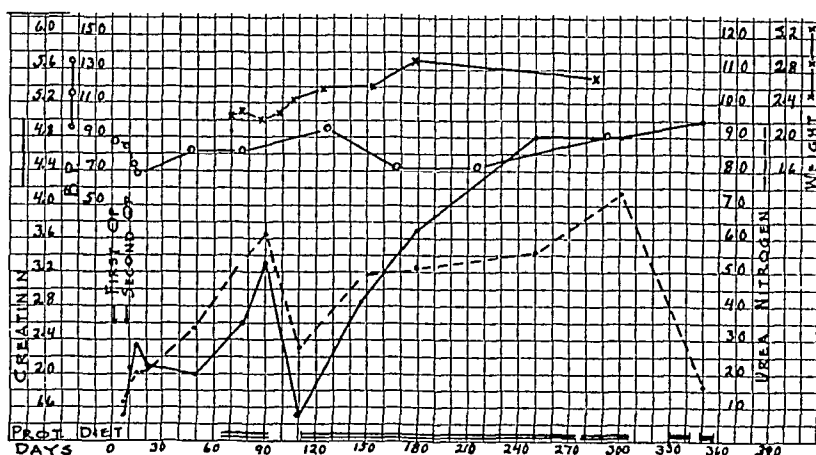


Fig 6—Findings in Experiment 40

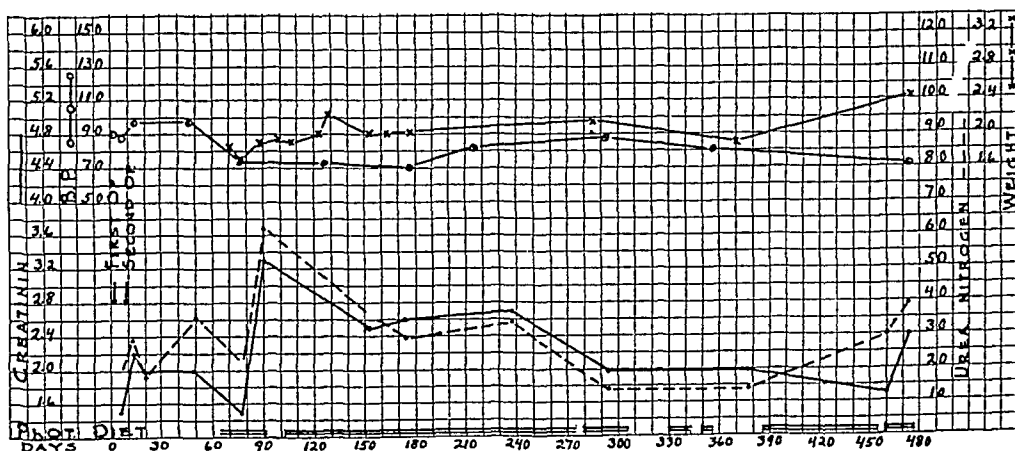


Fig 7—Findings in Experiment 41

EXPERIMENT 41 (Male, Fig 7)—Experiments were begun Aug 21, 1923, death occurred Jan 10, 1925, the four hundred and seventy-eighth day

Day 2, 255 Gm of the left kidney was removed, microscopically, this was normal except for occasional groups of lymphocytes

Day 9, the right kidney was removed, the weight was 8.05 Gm, microscopically, this was normal except for occasional groups of lymphocytes

Day 14, urine examination of a twelve hour specimen showed a volume of 120 cc, with specific gravity 1.012

Day 16, a twelve hour specimen showed a volume of 275 cc, with specific gravity 1.015

Day 85, a twenty-four hour specimen showed a volume of 335 cc, with specific gravity 1 024 and a slight trace of albumin

Day 182, the specific gravity of the urine was 1 025, albumin was absent

Day 299, a twenty-four hour urine specimen had a volume of 171 cc, with specific gravity 1 020 and albumin ++

Day 426, the fundi were normal

Day 437, a twenty-four hour urine specimen had a volume of 78 cc, with specific gravity 1 034 and albumin absent

Day 457, the fundi were examined by means of a red-free light. Nothing abnormal could be detected

Day 478, the animal was killed by a blow on the head, 469 days after the removal of the right kidney. The total number of days on a high protein diet was 325

At necropsy the right kidney was absent. The left weighed 102 Gm, the operative wound was healed, the remainder appeared normal. The aorta was normal throughout its length. The heart, which was normal, weighed 6 Gm. There was much omental, mesenteric and perirenal fat.

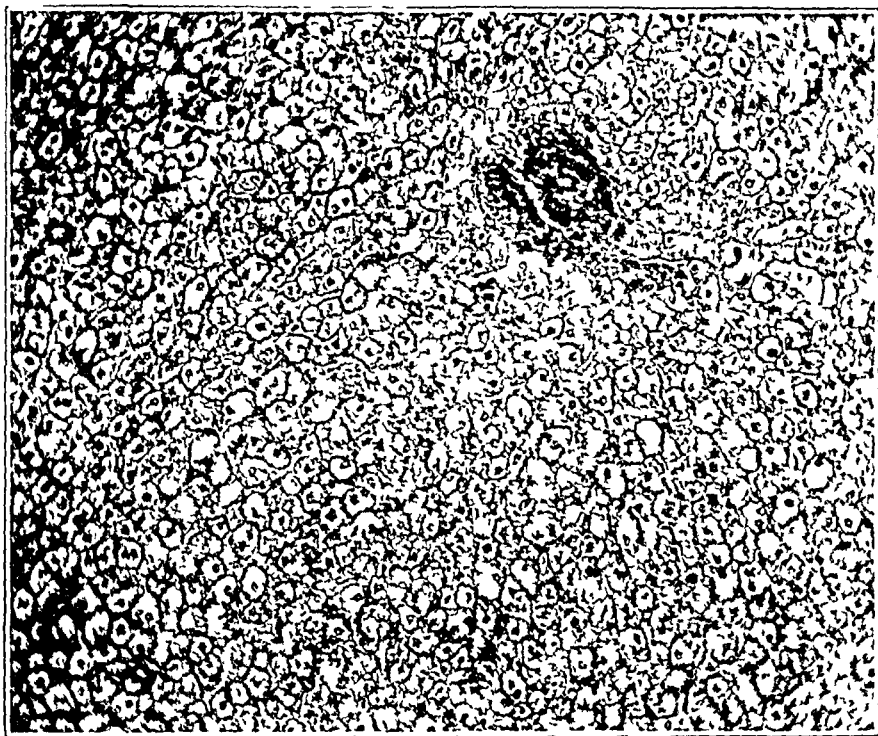


Fig 8 (Experiment 41) —Hydropic change in liver 469 days after removal of 65 per cent of the kidney substance and after 325 days on high protein diet

Microscopically, in the left kidney remnant there were a few lymphocytes about the operative scar, a few small areas of spontaneous nephritis and hypertrophy of the glomeruli and tubules. In the aorta there were degenerative changes in the media, with beginning calcification. In the liver there were hydropic change in the cells throughout the lobules and slight periportal infiltration of the lymphocytes (Fig 8).

The abnormal findings were degenerative changes in the media of the aorta and hydropic change in the liver.

EXPERIMENT 42 (Male, Fig 9) —The experiments were begun Aug 10, 1923, death occurred Jan 10, 1925, the five hundred eighteenth day.

Day 2, 50 per cent of the left kidney cortex was infarcted.

Day 30, a twenty-two hour urine specimen had a volume of 160 cc, with specific gravity 1 020, albumin was absent The right kidney was removed, microscopically, it was normal except for occasional groups of lymphocytes

Day 32, the urine specimen had a volume of 100 cc, with specific gravity 1 013

Day 33, a twenty-four hour urine specimen had a volume of 250 cc, with specific gravity 1 020

Day 184, the specific gravity of the urine was 1 027, albumin was absent

Day 221, calcium in the blood was 16 mg per hundred cubic centimeters

Day 234, the specific gravity of the urine was 1 036, albumin was ++

Day 308, a twenty-four hour urine specimen had a volume of 65 cc, with specific gravity 1 031 and albumin +

Day 466, the fundi showed no signs of arteriosclerosis or albuminuric retinitis

Day 484, a twenty-four hour urine specimen had a volume of 88 cc, with specific gravity 1 036, albumin was absent

Day 497, the fundi were examined by a red-free light but nothing abnormal was found

Day 518, the animal was killed by a blow on the head, 488 days after the removal of the right kidney The total number of days on a high protein diet was 325

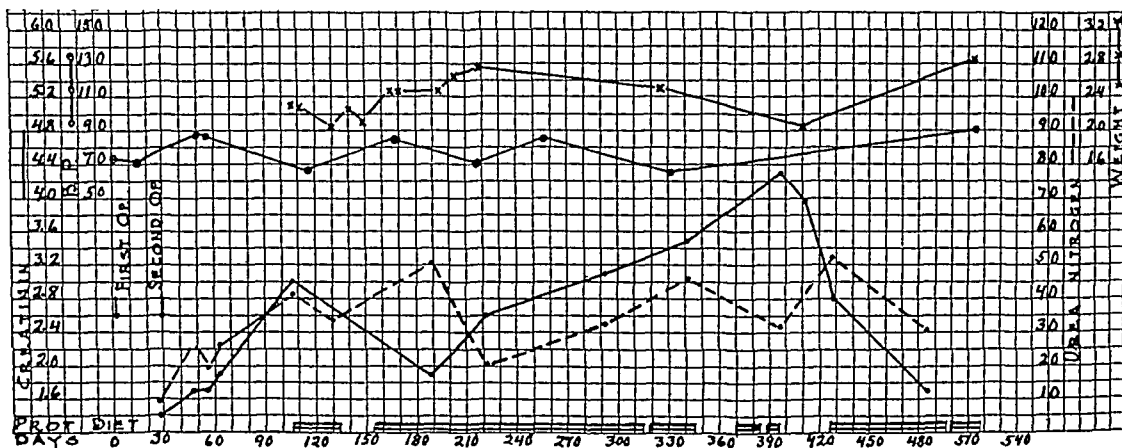


Fig 9—Findings in Experiment 42

At necropsy the right kidney was absent The left was bound down by adhesions, it weighed 91 Gm The infarcted areas were healed and one was completely calcified, the noninfarcted areas appeared normal The aorta was normal except for slight thickening about the mesenteric vessels

Microscopic examination of the kidney remnant showed small areas of spontaneous nephritis, otherwise it was normal The aorta was normal The liver showed marked hydropic change in the cells, which was greatest at the centers of the lobules

The abnormal findings were infarcts of the left kidney, one calcified, and hydropic change in the liver

EXPERIMENT 43 (Female, Fig 10)—The experiments were begun Aug 10, 1923, death occurred Jan 10, 1925, the five hundred twentieth day

Day 1, the animal was pregnant, and not yet fully grown

Day 2, 50 per cent of the left kidney cortex was infarcted

Day 27, a twenty-three hour urine specimen had a volume of 465 cc, with specific gravity 1 012, albumin was absent

Day 28, a twenty-five hour specimen had a volume of 245 cc, with specific gravity 1 024 (Table 4, Paper I)

Day 30, the right kidney was removed, the weight was 83 Gm, microscopically, it was normal

Day 34, a twenty-four hour specimen had a volume of 385 cc, with specific gravity 1010

Day 35, a twenty-four hour specimen had a volume of 400 cc, with specific gravity 1012, albumin was absent

Day 183, the specific gravity of the urine was 1025, albumin was absent

Day 226, the specific gravity of the urine was 1026, albumin was absent

Day 322, the animal delivered young, which were dead when found

Day 341, a twenty-four hour urine specimen had a volume of 195, with specific gravity 1019, albumin was ++

Day 376, the animal delivered young Three of this litter survived These were the only young to survive of all those delivered during the year 1924

Day 399, the animal delivered young, which died the same day

Day 468, the fundi were normal

Day 480, a twenty-four hour urine specimen had a volume of 198 cc, with specific gravity 1021 and albumin ++

Day 499, the fundi were examined with a red-free light, the vessels all appeared normal

Day 515, the animal was pregnant

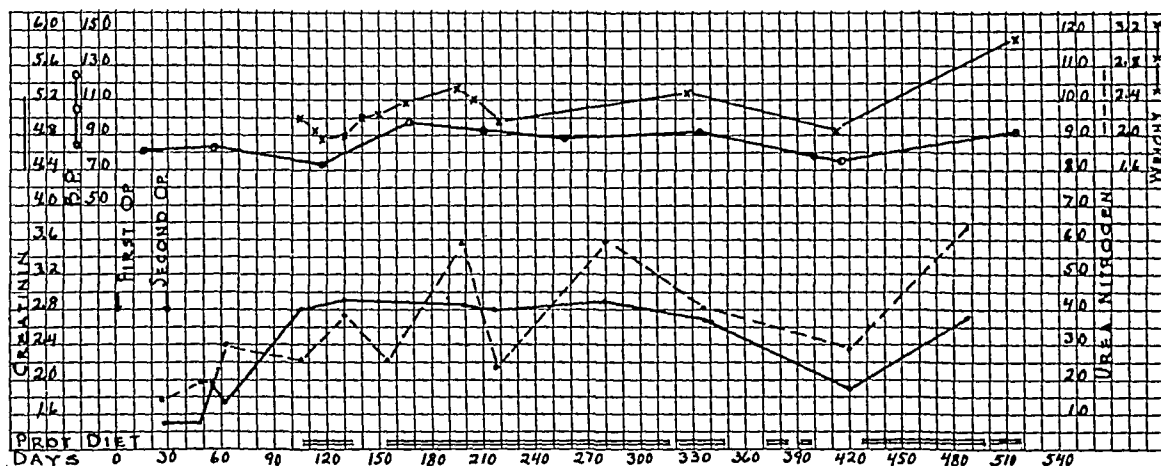


Fig 10—Findings in Experiment 43

Day 520, the animal was killed by a blow on the head, 490 days after the removal of the right kidney The total number of days on a high protein diet was 325

At necropsy the right kidney was absent The left was surrounded by large quantities of fat, the weight was 157 Gm, the capsule was adherent over the operative infarcts, the infarcted areas were calcified In the aorta there were a moderate number of atheromatous streaks and patches, and moderate sclerosis in the root The heart weighed 105 Gm, the pulmonary and aortic valves were both moderately thickened, the mammary glands contained milk

Microscopically, the left kidney infarcted areas showed complete atrophy, there were scars from the spontaneous nephritis, otherwise it was normal In the aorta there were marked atheromatous changes in the intima and beginning calcification in the media (Fig 11) The liver showed marked hydropic change

The abnormal findings were calcified infarcts in the left kidney, moderate atherosclerosis in the aorta and hydropic change in the liver

EXPERIMENT 44 (Female, Fig 12) —The experiments were begun Aug 8, 1922, death occurred Jan 10, 1925, the eight hundred eighty-seventh day (Table 4, Paper I)

Day 158, 235 Gm. of the left kidney was excised, microscopically, this was normal (Fig 13)

Day 165, the animal delivered young

Day 206, the right kidney was removed, the weight was 835 Gm, microscopically, it was normal

Day 246, the animal was placed on an egg and bean diet

Day 250, she looked ill and was replaced on a normal diet She had apparently eaten little of the beans and eggs

Day 258, the animal looked extremely sick and had rigors

Day 258, albumin was +, there were many hyaline casts and occasional red blood cells in the sediment The diagnosis was pyelonephritis

Day 261, albumin was absent, the sediment contained a moderate number of hyaline casts and pus cells Methenamine was administered in the drinking water

Day 264, albumin was absent, the sediment contained a moderate number of hyaline casts and pus cells Methenamine was administered in the drinking water

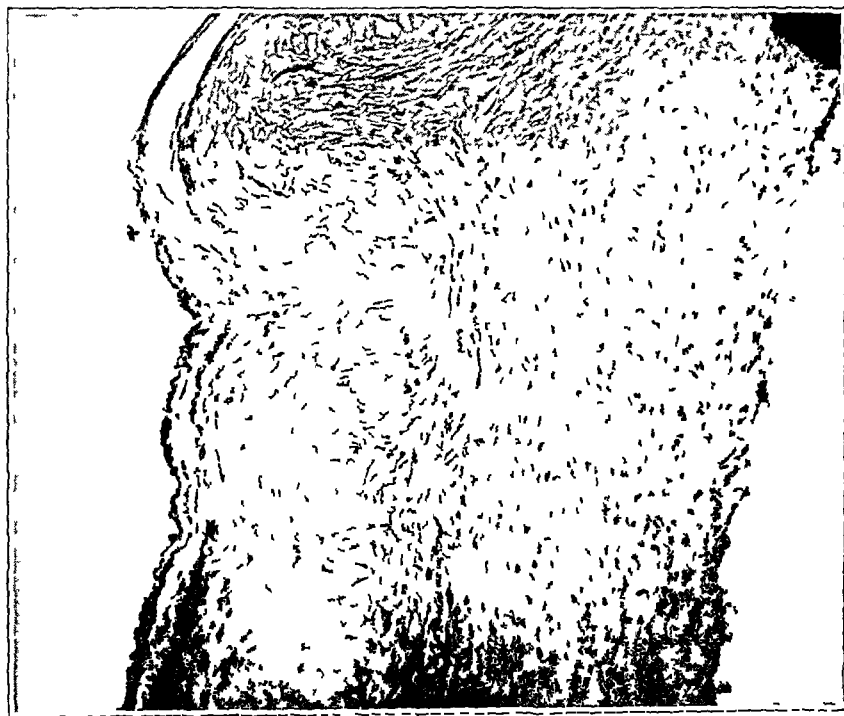


Fig 11 (Experiment 43) —Aorta 490 days after removal of right kidney and after 324 days on high protein diet, marked atheromatous change in the intima, 65 per cent of kidney substance removed

Day 266, albumin was absent, casts and pus were absent The animal appeared much better and was replaced in the cage with the other rabbits

Day 271, she appeared thin but lively The fundi showed nothing abnormal

Day 275, the urine specimen had a volume of 56 cc, albumin was absent, specific gravity was 1.035

Day 279, the urine specimen had a volume of 310 cc, with specific gravity 1.010

Day 284, the animal was still very thin, and was pregnant

Day 439, she delivered young

Day 539, in the urine specimen albumin was +, specific gravity was 1.012, there were many pus cells in the sediment

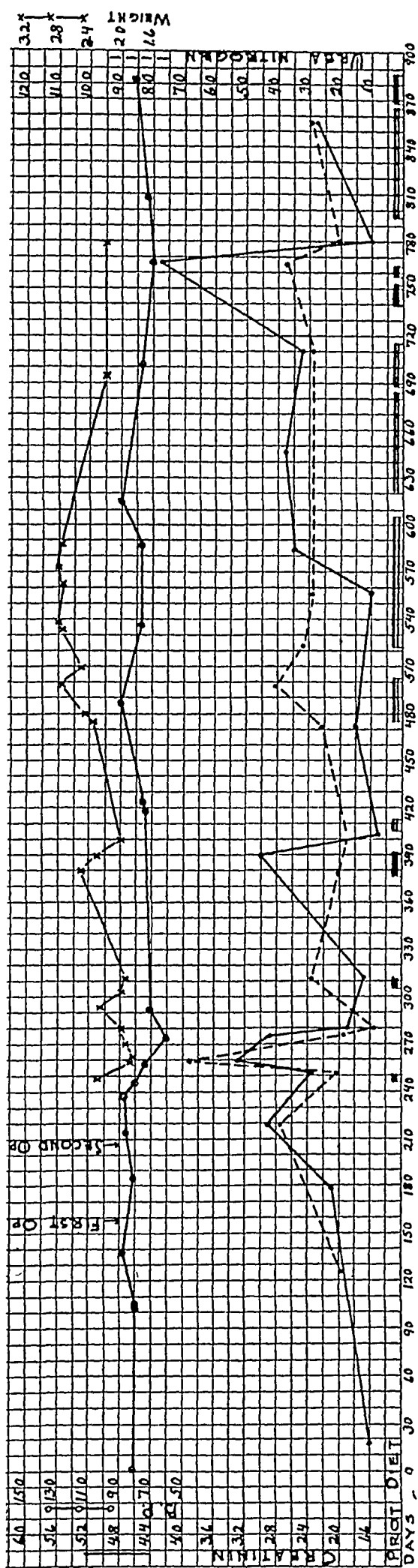


Fig 12—Findings in Experiment 44

Day 540, albumin was + + +, specific gravity was 1 016, there were many pus cells in the sediment

Day 600, the urine specimen showed albumin + and specific gravity 1 031, the sediment contained a few pus cells

Day 607, the animal delivered young She bled from the genital tract until Day 614 She became extremely ill during this time, but grew better rapidly as soon as the bleeding stopped There was apparently some injury to the birth canal and rectum at the time of this delivery The mucous membrane was observed to protrude at times and the parts always remained soiled thereafter

Day 630, the right eye showed a purulent discharge originating in some lacerations of the eyelids

Day 667, a twenty-four hour urine specimen had a volume of 265 cc, there was a trace of albumin, specific gravity was 1 021, the sediment showed nothing abnormal



Fig 13 (Experiment 44) —Section of wedge removed from left kidney at first operation, same magnification as Figure 14

Day 669, a twenty-four hour specimen had a volume of 460 cc, albumin was +, specific gravity was 1 023, the sediment contained nothing abnormal

Day 779, the animal was pregnant

Day 835, the fundi were examined for signs of arteriosclerosis and albuminuric retinitis, nothing abnormal was found

Day 848, a twenty-four hour urine specimen had a volume of 151 cc, albumin was +, specific gravity was 1 032, the sediment contained only triple phosphate crystals and epithelial cells

Day 866, the fundi were examined with red-free and with white light, nothing abnormal was found

Day 868, the animal delivered young, one of which lived for twenty-four hours The remainder died promptly

Day 887, she was killed by a blow on the head, 681 days after the removal of the right kidney The total number of days on a high protein diet was 341

At necropsy the right kidney was absent. The left was surrounded by a large quantity of fat and was bound down by adhesions, the weight was 12.25 Gm, the cortex appeared wider than usual. The scar of operation was healed, the pelvis was normal. There were many atheromatous patches throughout the aorta, two dilatations with thinning of the wall being present in the thoracic portion. The entire vessel appeared widened. The heart, which weighed 9.1 Gm, was normal. The liver was normal. There was much omental, mesenteric and perirenal fat. The ovaries contained a number of small cysts.

Microscopically, the remnant of the left kidney showed marked hypertrophy of the glomeruli and tubules (Fig 14). In the aorta there were marked atheromatous change in the intima and calcification in the media. The liver showed marked hydropic change, marked periportal infiltration of lymphocytes and some hyperplasia of the biliary ducts.



Fig 14 (Experiment 44) —Remnant of left kidney 681 days after removal of right kidney and after 341 days of high protein feeding, hypertrophy of glomeruli and tubules (comparison should be made with Figure 6)

The abnormal findings were hypertrophy of the left kidney, atherosclerosis with dilatation of the aorta, hydropic change in the liver, with biliary duct hyperplasia.

PROGRESS OF THE DIET GROUP

Rabbits 29 to 44 compose the diet group (Group 3). The group consumed a total of 522 pounds (236.8 Kg) of roundsteak. The daily consumption averaged 87.2 Gm per rabbit, or about 4 per cent of the body weight.

Rabbits 32 to 44 were all operated on. All recovered and in most cases were allowed to eat a normal diet until the concentration of the metabolites in the blood had returned to normal.

Rabbits 32 to 35 were operated on only once and deprived of 12 per cent or 50 per cent of kidney substance. These did not show an increase of creatinin above normal limits.

Rabbits 36 to 44 were subjected to removal of from 62 to 68 per cent of kidney substance. There was a moderate postoperative increase in blood metabolites. The creatinin values lay between 2.36 and 3.0 mg per hundred cubic centimeters. The urea values rose to from 28 to 42 mg per hundred cubic centimeters but were somewhat inconsistent. The return to normal values occurred in a time varying from twenty-six to 390 days.

The first rabbits given a high protein diet (Rabbits 36, 38 and 44) received the whites of hard boiled eggs after Newburgh and Clarkson.³ They all refused to eat until driven by hunger. They fasted for several days before eating. All lost weight rapidly. All became constipated, passing only small amounts of feces once every two or three days. Rabbit 38 fasted for six days and at the end of that time was given a normal diet. It had eaten no egg whatever but showed some albumin in the urine and the sediment contained casts.³ It lost 10 per cent of its body weight. Following this a normal rabbit was fasted two periods of five days each to determine the effect on the urine. Albumin was present on the fourth and fifth days in the first period and on the third day in the second period. These few observations prove nothing but indicate that the results of Newburgh and Clarkson may have been at least partially inanition phenomena or the results of constipation.

Rabbits 38 and 44 were later fed the meat bread constituting the high protein diet of this study. Whereas both lost weight on the egg diet both gained while eating the meat bread.

Weight—In all experiments in which a number of weight determinations were made the animals exhibited a gain, except Rabbits 37 and 38 (protocols). These two lost slightly. In four others (Rabbits 32 to 35) the weights were disregarded as unreliable.

The ten animals which were still alive at the close of the experiments and which were killed had all been on the high protein diet until within twenty-four hours of death. All were fat. Each contained large deposits of fat in the omentum, mesentery and perirenal tissues. It cannot, therefore, be argued that any of the findings here recorded were due to inanition.

Blood Metabolites—Many writers have described a rise in blood urea values following a high protein diet.⁹ Such a rise occurred in the animals that were operated on. Subgroup D (65 per cent removed) ranged from normal to 74.8 mg per hundred cubic centimeters of blood,

⁹ Chace and Rose, Folin, Denis and Seymour, and McLean (Footnote 5, first, second and third references)

Subgroup C (50 per cent removed) up to 43.4 mg, Rabbit 33 in Subgroup B (12 per cent removed) showed 35 mg per hundred cubic centimeters

I have not seen described any similar rise in creatinin. In fact, the concentration of creatinin is said to be independent of the diet. In these experiments the creatinin also rose to high levels, which were maintained consistently. In fact, the creatinin was found to be a much more reliable index than the urea nitrogen, although somewhat less delicate.

The amount of kidney substance functioning seemed to determine definitely the concentration of the metabolites when the diet was given. Hewlett¹⁰ and Chace and Rose¹¹ describe a rise in the concentration when much protein is given in the diet but do not make entirely clear the matter as to whether this rise occurs in normal individuals or only in those which are known to have a lowered renal function. McLean⁹ states that the level is higher in nephritis than in normal persons but does not definitely say whether there is a rise in normal individuals.

The results of these experiments are definite on this point. The control animals not operated on showed no rise of either urea nitrogen or creatinin even after long periods of time on the diet (Rabbits 29, 30 and 31, Figs 1 and 2). Only the animals having a reduced kidney filter showed a rise in concentration of metabolites. The rise was proportionate to the amount of kidney substance removed.

The rise appeared even in the case of Rabbit 32 from which only 12 per cent of the kidney substance had been removed. The urea nitrogen rose to 35 mg after five days on the protein diet and twelve days after the operation. The blood of Rabbit 33 (the other rabbit in Subgroup B) unfortunately was not examined until nineteen days after operation. If there had been a rise in the first two weeks, the values had returned to normal when the blood was examined. It is possible that the hypertrophy which is known to occur may overcome entirely deficiencies as small as 12 per cent.

The two animals in Subgroup C (50 per cent of kidney removed) both showed definite rises in the values of both creatinin and urea. These values were intermediate between those obtained in Subgroups B and D. The creatinin in the case of Rabbit 34 rose to 1.8 mg, in Rabbit 35 to 2.5 mg. The urea nitrogen in Rabbit 34 rose to 35.2 mg and in Rabbit 35 to 43.4 mg (Table 1).

Subgroup D (Rabbits 37 to 44, 65 per cent plus removed) gave the highest values, having lost most kidney substance (protocols and charts). The creatinins varied from 2.5 to 4.3 mg and the urea nitro-

10 Hewlett, Gilbert and Wickett (Footnote 5, fourth reference)

11 Chace and Rose (Footnote 5 first reference)

gen from normal to 74.8 mg while on the protein diet, yet the animals all appeared healthy and were active at all times. Rabbits 39 and 40 eventually developed calculi and hydronephrosis and exhibited much higher values, but remained in good health until these complications intervened.

All groups returned to normal or to much reduced concentrations each time that a normal diet was substituted. It usually required only a few days for this change to take place, and again only a few days for a return to high levels when the protein diet was given.

These findings indicate that the removal of the kidney substance raises the threshold values of creatinin and urea. The rise in the threshold varies directly with the amount removed.

Blood Pressure—The blood pressure in the diet group did not vary from that of the controls that were operated on. In general, the blood pressure of all the animals remained within normal limits at all times whether they were on a normal or a protein diet, irrespective of the amount of kidney tissue functioning (protocols and charts of Rabbits 29 to 44). Even in the case of Rabbit 44, which survived an attack of pyelonephritis, there was no hypertension (protocol of Day 258).

It seems certain that neither a reduction of the kidney nor a high concentration of urea and creatinin in the blood raises the blood pressure. It is inferred that when hypertension occurs in chronic glomerulonephritis, there is some other factor acting to cause the increased blood pressure.

Fundi—The fundi were examined from time to time as in the controls operated on. In addition to the usual examination with the Welch-Allyn ophthalmoscope, the red-free light¹² was used in ten cases (Rabbits 30 to 35 and 42 to 44). None of the common signs of arteriosclerosis or albuminuric retinitis were observed at any time by either method.

Urine—There were no striking urinary changes following the high protein feeding. Seven of the sixteen diet animals showed albumin on different occasions. These seven were Rabbits 30 (normal control) and 39 to 44. The amounts were small except in the case of Rabbit 44, which at one time developed a pyelonephritis with pus and blood in the urine. Usually albumin was absent.

Pregnancy—The females all became pregnant frequently. In general, they carried their litters to term, but the young did not live after delivery. During the time when the diet experiments were carried out (over a year) only three young survived. These were delivered by

¹² Vogt, Alfred. Ueber eine vertikale Streifung, welche an der Vorderfläche der Netzhaut junger Individuen im Rotfreien Licht wahrgenommen wird. Klin. Monatsbl. f. Augenh. 60: 47, 1919.

Rabbit 43 Every effort was made to keep the young alive but, with the exception just mentioned, all died in from twenty-four to forty-eight hours

The reason for the failure of the young to survive is not clear It may be that the diet was lacking in some essential factor although it was thought to be complete when first prepared

The fresh lettuce given at weekly intervals contained vitamins A, B and C but may have been insufficient in quantity to supply the young with necessary accessory food factors The lean beef used contained all three of these vitamins but at least the antiscorbutic factor was destroyed by the baking This factor was probably absent entirely from the meat bread and supplied only by the lettuce¹³

NECROPSY FINDINGS

Kidney—Rabbits 39 and 40 died from obstruction by renal calculus These showed hydronephrosis grossly, and microscopically gave the typical picture of obstruction No microscopic examination was obtained in the case of Rabbit 29

The kidneys of the remaining thirteen in the diet group were carefully examined both grossly and microscopically The only significant change found was hypertrophy

Hypertrophy occurred in all Even the kidneys taken from the controls that were not operated on (Rabbits 30 and 31) were hypertrophied

The average weight of twenty-six normal kidneys removed in toto at operation was 9 Gm Only three weighed as much as 11 and one only as much as 13 Gm The average weight of the two kidneys removed from Rabbit 30 at necropsy was 11.5 Gm The weight of the right and the left kidneys from Rabbit 31 averaged 14.2 Gm (Table 4)

The left kidney was removed in part or completely from Subgroups B and C At necropsy the weights of the right kidneys averaged 12.5 Gm, which represents a distinct hypertrophy

In Subgroup D the kidney remnants of six of the nine weighed as much or more than the other kidney previously removed in toto In the cases of Rabbits 43 and 44 the hypertrophy was great, in both cases estimated at more than 100 per cent

Hypertrophy also occurred in the controls that were operated on For that reason it is clear that a degree of hypertrophy follows the operative reduction That the diet has an added effect also seems reasonably certain The hypertrophy in general was greater in the diet animals

¹³ Owing to the erection of a new hospital building during this time the animals were kept in temporary pens unsuited to the raising of young This may have been a factor in the death of the young

than in the operated controls and moreover the controls not operated on which ate the protein diet developed hypertrophy

Microscopically, there was no evidence of tubular or glomerular injury resulting from the diet. The operative specimens were examined in all cases and compared with the portions removed at necropsy, in some cases more than two years later. The same kidney (left) was available for microscopic study both before and after the diet experiments in most cases. Unless complications had intervened, there were no changes except hypertrophy and, in some cases, an increase in the extent of spontaneous nephritis.

Figure 13 is a photograph of the wedge removed from the left kidney of Rabbit 44 on Day 158. Figure 14 shows a section from the remnant of the left kidney found at necropsy 729 days (two years)

TABLE 4—*Summary of Operative Procedures and Necropsies in Diet Animals*

Rabbit	Days Survived After Operations	Days on High Protein Diet	Weight of Piece of Left Kidney Excised	Weight of Right Kidney Excised	Percentage of Kidney Substance Remaining	Weight of Remnant of Left Kidney	Microscopic Findings in Remnant
29		48			100		
30		357		11.4	100	11.6	Normal
31		324		14.5	100	13.9	Normal
32	63	52	1.85	10.7	88	5.9	Normal
33	90	52	1.9	12.4	88	8.4	Normal
34	97	88		14.7	50	9.1	Normal
35	113	88		12.3	50		Pigment in medulla
36	64	5	Infarct	11.9	35*	7.8	Normal
37	160	23	Infarct	8.2	35*		
38	449	17	2.0	7.3	36		
39	301	128	Infarct	11.4	35*	11.5	Hypertrophy of tubules and dilatation
40	348	238	2.3	8.3	36	14.5	Pyelonephritis
41	469	325	2.55	8.05	34	10.2	Hypertrophy of tubules and glomeruli
42	488	325	Infarct	7.1	35*	9.1	Normal
43	490	325	Infarct	8.3	35*	15.7	Hypertrophy of tubules and glomeruli
44	681	341	2.35	8.35	35.9	12.25	Hypertrophy of tubules and glomeruli

* Approximate only

after operation. The remnant had carried on the work of both kidneys for 681 days and had been subjected to the effects of protein feeding for 341 days. There was a marked hypertrophy of the glomeruli and tubules but no other change.

The increased number of scars from spontaneous nephritis found at necropsy is explained on the basis of the increase in age of the animals.

Aorta—In the vascular system the only pathologic condition found was confined to the aorta and the aortic valves. The lesion found was a marked atherosclerosis.

This sclerosis did not extend to the small arteries or arterioles. The small arteries and arterioles of the lungs, heart, liver, spleen, small intestines, kidneys, tubes, ovaries and voluntary muscle were carefully examined in each case for thickening and degeneration. None was

found. This fact may explain the lack of fundus changes and the failure of the blood pressure to rise. Hypertension in case of human nephritis appears in those cases which develop sclerosis in the smaller vessels. The fundus changes in nephritis, according to Umber,¹⁴ are due to vascular disease and these changes would not occur in the presence of normal vessels.

The aorta was carefully described in thirteen of the sixteen in the diet group (protocols). Four contained extensive and marked lesions. Four showed a moderate atheromatous change with occasional small spots of calcification. Four were normal, one other was nearly normal.

In the case of Rabbit 39, the aorta was dilated through the greater portion of its length and was so calcified that it fractured repeatedly during the manipulations necessary to remove it. In Rabbits 31 and 44 localized dilatations developed. These were in fact broad, shallow, saccular aneurysms. In both cases these dilatations occurred in calcified areas located in the arch or upper thoracic aorta.

The sclerotic changes in the aorta did not seem to bear any relation to the amount of kidney substance functioning. Two of the normal aortas were found in Subgroup D (65 per cent removed), one in Subgroup C (50 per cent removed) and one in Subgroup B (12 per cent removed). Both of the controls not operated on presented sclerosis. In one of them (Rabbit 31, Fig. 3) the disease was far advanced, just as far advanced as in Rabbit 43, which had undergone both operations (Fig. 11).

The length of time on the protein diet seemed to bear a direct relation. In general, the extensive changes occurred in those which had eaten meat bread over a long period of time. This did not hold true in each case. Rabbits 41 and 42 were both on the protein diet for 325 days. Neither developed much injury. The aorta in the former was only moderately pathologic and in the latter was entirely normal. Such variations as these are best explained on the ground of individual susceptibility.

The pathologic changes were typical, microscopically, of arteriosclerosis. The atheromatous areas proved to be composed of swelling, fatty deposits and degenerative changes in the intima. The calcium deposits lay in the media. In many areas, the media contained degenerated fibers with, as yet, no deposit of calcium (Figs. 11 and 3). Newbough and Clarkson³ have described similar changes after protein feeding.

The controls operated on developed no aortic lesions, even those which died from renal insufficiency. This fact indicates that the marked arteriosclerosis found in the diet animals was due to the diet. It can-

¹⁴ Umber, F. *Heutige Standpunkt in der Pathologie und Therapie der Nierenkrankheiten*, Deutsch. med. Wchnschr. **49** 369 (March 23) 1923.

not be argued with certainty that the protein caused the damage because there are other possible factors which have not been controlled. It is even possible that we are dealing with a deficiency disease.

Liver—The liver was found to be pathologic in all of the diet animals except in the case of Rabbit 36, which had been on the diet only five days.

The changes in all cases were microscopic and in most were represented by a hydropic condition of the liver cells. This was in contrast to the fatty metamorphosis found in the liver cords in a number of the controls operated on. The hydropic change was most marked at the centers of the lobules, but in many included the entire lobule (Rabbits 30 and 32) and was extensive in the extreme. Its exact nature and cause is not clear. It occurred in both the animals operated on and those not operated on and is considered a result of the diet.

Rabbit 35 presented fatty change and Rabbit 39 a number of areas of necrosis. The necrosis was at the centers of the lobules. In Rabbit 40 there was a periportal lymphocytic infiltration. This could be explained on the basis of the pyelonephritis which accompanied the hydronephrosis in this case.

SUMMARY

The purpose of this study was (*a*) to determine the blood pressure changes in low renal function or insufficiency and (*b*) to determine the possible influence of high or low protein diet on the course of chronic renal disease.

Thirty-eight rabbits were operated on before any were placed on a high protein diet. Of these twenty-nine died without having been on a protein diet. All except four showed microscopic or gross signs of obstruction at necropsy.

The four that died of renal insufficiency without signs of obstruction all showed diffuse hydropic change in the kidney remnant. This change was most extreme in two cases. It is considered that this hydropic degeneration represents the results in the kidney of renal insufficiency without other complications. It is probably due to overactivity.

Following the operative procedures in which over 60 per cent of kidney substance was destroyed, there was a retention of creatinin and urea nitrogen in the blood. This became progressively greater until death in those which died, but decreased in those which recovered until the values again became normal.

There was no increase in the blood pressure following the reduction of kidney substance, even in those which died from a slowly progressive renal insufficiency.

A high protein diet containing over 30 per cent of protein was fed to sixteen rabbits over a long period of time, in a number of cases about a year. Three of these rabbits had not been operated on, two had

lost 12 per cent of kidney substance, two had lost 50 per cent and the remaining nine had lost from 60 to 70 per cent of kidney substance

The only change observed in the kidneys which might be attributed to the diet was a hypertrophy. There were no degenerative or inflammatory changes found except those of spontaneous nephritis.

All the diet animals showed approximately normal concentrations of blood metabolites when the high protein feeding was begun. The normal controls developed no increase while on the diet. All the animals operated on developed a retention of creatinin and urea nitrogen the degree of which was proportionate to the quantity of kidney substance removed.

The high concentration of the metabolites did not seem to injure the health of the rabbits. They seemed to thrive on the diet. The young, however, did not survive.

There was no increase in the blood pressure during the periods when high protein diet was given.

The liver in all the diet animals showed an extensive hydropic change. The cause of this change is not clear.

The aorta in many showed signs of extensive atherosclerosis, with thinning of the walls, dilatation and calcium deposits.

CONCLUSIONS

1 Removal of two thirds of the kidney substance in rabbits results in a retention in the blood of urea and creatinin, which either increases progressively in intensity until death results, or decreases progressively until normal values are once more attained.

2 If the renal insufficiency is not progressive, the kidney remnant undergoes hypertrophy.

3 A high protein diet causes hypertrophy of the kidneys in normal rabbits not operated on.

4 A high protein diet causes no further change in the kidney remnant than to further augment the hypertrophy.

5 A high protein diet causes a retention of creatinin and urea in the blood in rabbits from which a portion of kidney substance has been removed. It is proportionate to the amount of kidney which has been removed. The retention does not occur in normal rabbits.

6 Hypertension is not caused in rabbits by renal insufficiency per se, nor by a high protein diet even in the presence of a low renal function, nor by prolonged retention of creatinin and urea in the blood.

7 The high protein diet here given results in a marked atherosclerosis of the aorta which does not extend to the small arteries. These changes in the aorta do not result from low renal function or from prolonged retention of creatinin and urea in the blood.

HEMOCHROMATOSIS AND CHRONIC POISONING WITH COPPER *

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Hemochromatosis is not so rare a disease as is generally supposed but the clinician has difficulty in recognizing it until the final stage when the three characteristic signs, cirrhosis of the liver, diabetes mellitus and pigmentation of the skin, are all evident. As for the earlier stages even the pathologist may occasionally overlook them.

This paper will consist of a general introduction to the subject of cirrhosis, of which pigment cirrhosis forms one type, and then of a discussion of different aspects of hemochromatosis under three headings, which are arranged in logical order although this is not the way in which the work was originally done. I had been trying for many years to discover the cause of so-called alcoholic cirrhosis. While testing out the injurious action of copper, among many other sub-

Incidence and Classification

	Number	Per Cent
Postmortem examinations (more than 1,000 in children)	5,400	
Well marked cases of cirrhosis	250	4.63
Classification of Cirrhoses		
1 Alcoholic cirrhosis	114	45.60
2 Pigment cirrhosis	19	7.60
Types 1 and 2 combined (the lesions of alcoholic and pigment cirrhosis both present)	50	20.00
3 Syphilitic cirrhosis	15	6.00
4 Infectious cirrhosis	13	5.20
5 Toxic cirrhosis	10	4.00
Old healed cirrhosis type not determinable	29	11.60

stances, I found that with it I could produce pigmentation and cirrhosis of the liver in rabbits in from three to twelve months, according to the size of the dose. This observation led to a more thorough histologic study of the lesions of hemochromatosis and later to a search for possible sources of copper poisoning to which man might be exposed.

TYPES OF CIRRHOSIS

An analysis of all the cases of cirrhosis of the liver which have come to postmortem examination at the Boston City Hospital during the last twenty-eight years shows that they can be divided into five different types, each with its own characteristic primary cell lesion and resulting gross appearance. The accompanying table shows the number of cases available for study and the frequency of occurrence of each type.

* Tenth Mellon Lecture before the Society for Biological Research of the University of Pittsburgh School of Medicine, April 30, 1925. Repeated as Hanna Lecture at the one hundred and eighty-third regular meeting of the Clinical and Pathological Section, Academy of Medicine of Cleveland, May 1, 1925.

A brief survey of the various kinds of lesions terminating in cirrhosis will make the subject of hemochromatosis easier to understand and more interesting. The different types will be presented not in the order of their frequency but from the pathogenic point of view. The first two are of infectious origin. By this term I mean that the microorganisms causing them are present in the lesions. The other three are due to injurious chemical agents brought to the liver by the blood.

Infectious Cirrhosis, Biliary Cirrhosis—The first type is due to ascending infection of the bile ducts by the colon bacillus (perhaps also sometimes by related organisms) which gives rise to a cholangitis.



Fig 1 —Acute cholangitis

The bacilli spread quickly throughout the liver causing acute inflammation within and around the bile ducts with destruction of the adjoining liver cells and fibroblasts of the stroma, followed by active regeneration of the connective tissue cells. In the early stages of the process the liver may be doubled in size. Obstruction of the bile ducts by exudate leads quickly to jaundice. The organisms may die out and repair with contraction of the liver follow. Sometimes the process recurs.

In the early stages the surface of the liver is smooth later it becomes finely granular. The most distinctive and characteristic feature of the later stage of the lesion is the broad zone of connective tissue

around the portal vessels, the liver cells around the hepatic veins in the centers of the lobules at the same time being intact. The original lobulation is not lost as it is for example in alcoholic cirrhosis.

This type of cirrhosis is comparatively rare so that a series of cases for special study, especially from the pathogenic point of view, is difficult to obtain. It seems probable, judging from the clinical descriptions of his case, that this is the variety of cirrhosis described by Hanot and known under his name. From the pathologic descriptions of his livers nothing can be made out and so far I have been unable to obtain from any pathologist in France a section of what he regards as Hanot's cirrhosis.

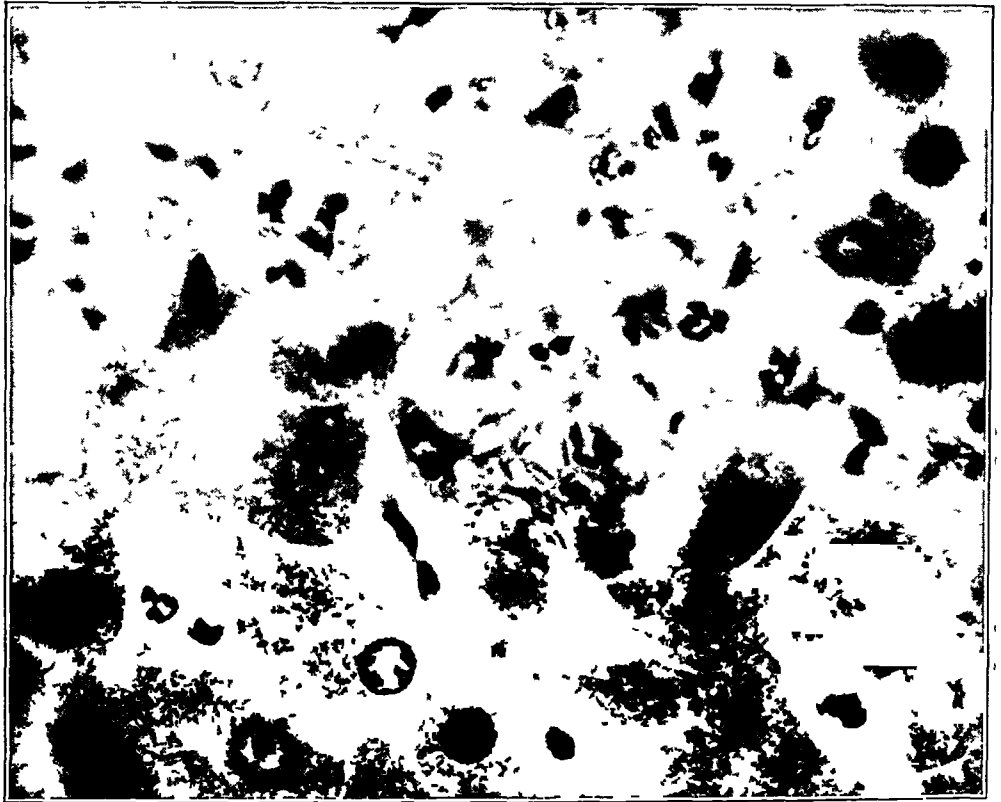


Fig 2—Colon bacillus invading liver lobule, necrosis and acute inflammatory reaction

Syphilitic Cirrhosis—This type is due to the presence of *Spirochaeta pallida* in the lesions. The injurious action of the organism is exerted chiefly or entirely on the fibroblasts of the stroma. Necrosis and regeneration of the connective tissue cells occur, followed by contraction of the collagen fibrils and compression, atrophy and disappearance of the included liver cells. The result is a more or less diffuse sclerosis. The lesion is complicated, occasionally in congenital syphilis, quite regularly in the acquired disease, by proliferation of the intimal tissue in arteries leading to obliteration of the lumen, followed by

necrosis (infarct, commonly called gumma) of the tissue no longer supplied with blood. Organization of multiple necrotic foci by granulation tissue followed by contraction causes deep scars which sometimes divide the liver into many lobes. The condition is characteristic and is recognized in the appropriately descriptive term *hepar lobatum*, in my experience, at least, a comparatively rare condition.

I was called over to the surgical amphitheater one day before Dr. Lahey's fourth year class. He was operating on a woman for ulcer of the duodenum, a diagnosis made by certain students who had examined the patient and concurred in by him. Nothing was found at operation except an unusual condition of the liver which he had never

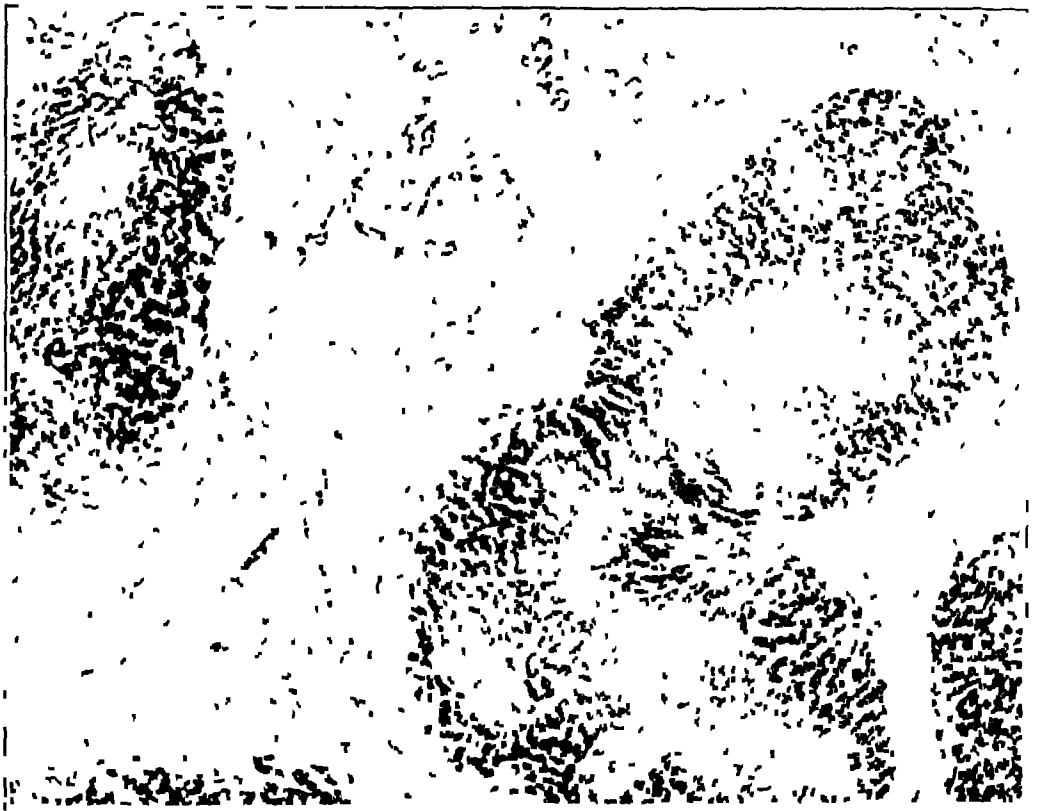


Fig. 3—Biliary cirrhosis, lesion located around bile ducts; liver cells around hepatic veins intact

seen and did not recognize. After examining the liver tissue through the incision I asked what the Wassermann test had been. "Negative," the class answered. I took another look and said that the appearance was typical of syphilis of the liver and could be due to nothing else. I asked Dr. Lahey to cut me out a piece, not from an elevated part but from a scar. He answered that he didn't like to but that he would. On one face of the wedge shaped piece excised I was able to show to the class at once a small, healing gumma and on the other side two. On my return to the laboratory I sent over to the clinic

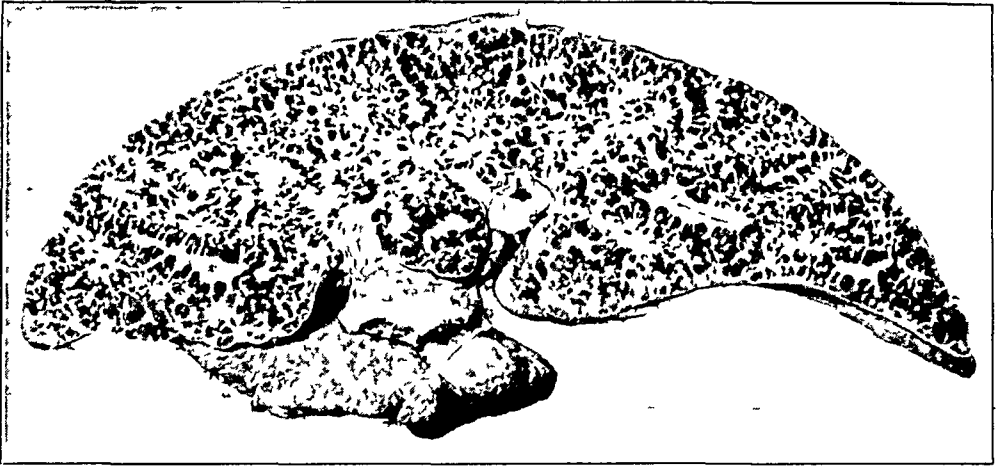


Fig 4—Biliary cirrhosis , gross appearance externally and on section



Fig 5—Masses of *Spinochaeta pallida* in connective tissue stroma of liver causing sclerosis in a new-born child

a photograph of a typical case of hepar lobatum in order to impress the lesion more deeply on the students

The three other types of cirrhosis are of toxic origin

Toxic Cirrhosis, Cirrhosis of Acute Toxic Origin—A variety of injurious agents can cause this type of cirrhosis, for example, phosphorus, arsenic (frequently following treatment with arsphenamin), chloroform, carbon tetrachloride and the toxin derived from certain streptococci. The destructive lesion, extensive necrosis of the liver cells, appears to be always of acute origin. The necrosis affects first the cells in the centers of the lobules and spreads peripherally. If the lesion is not too extensive (central necrosis), removal of the necrotic

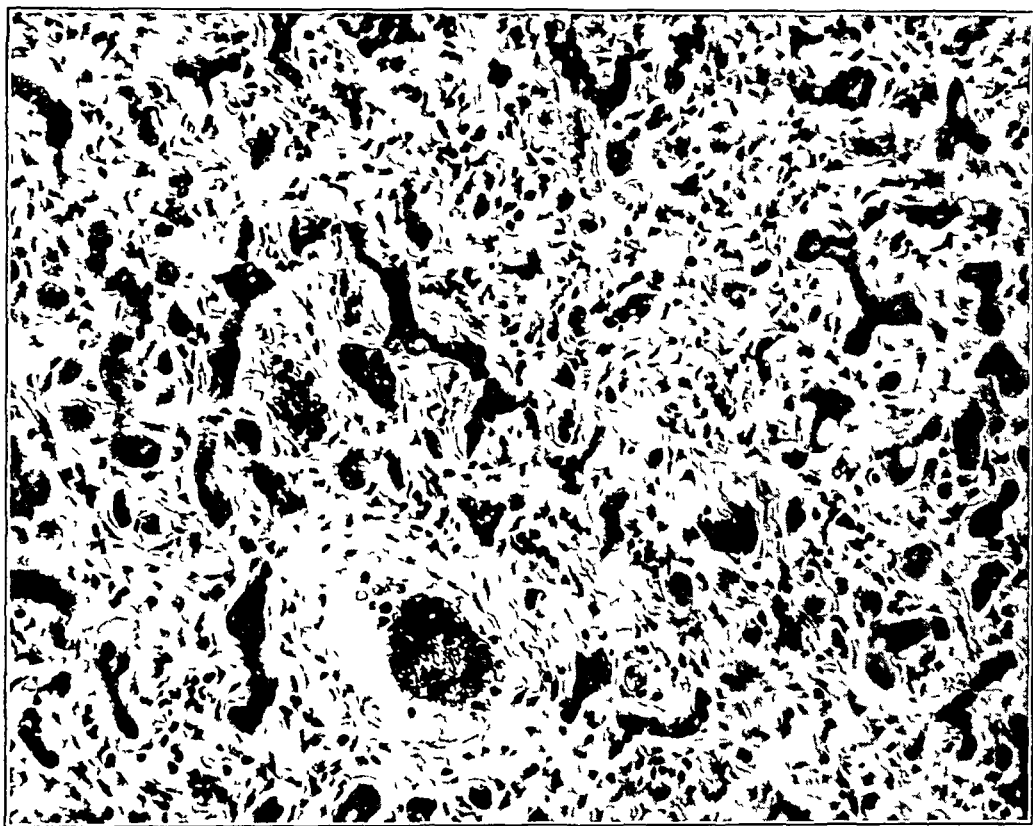


Fig. 6—Diffuse sclerosis of liver due to acquired syphilis in an adult

cells and regeneration of them may occur within ten days. If all the cells in a lobule are killed, no regeneration of liver cells takes place. The bile duct epithelium proliferates to a slight extent and then stops. It cannot form liver cells. They can regenerate only from liver cells.

In cirrhosis of acute toxic origin all the liver cells in many lobules may be destroyed. After the necrotic cells have been removed through the digestive action of leukocytes, these foci of stroma, sinusoids and bile ducts shrink (acute red atrophy). In other foci where liver cells remain rapid regeneration takes place and the new formed liver cells are stained yellow by bile.

Next to the syphilitic liver the liver of acute toxic cirrhosis may present the greatest irregularity of surface, projecting nodules of all sizes due to regeneration of liver cells and depressed areas due to condensation of stroma where the cells have disappeared, but there is never the deep scarring which results from organized gummas. At other times the liver may closely resemble that of alcoholic cirrhosis but the nodules are usually more irregular in size.

Excessive regeneration of liver cells sometimes results in the formation of nodules one or more centimeters in diameter which have been called adenomas. In these nodules no lobular arrangement is evident and bile ducts are absent.

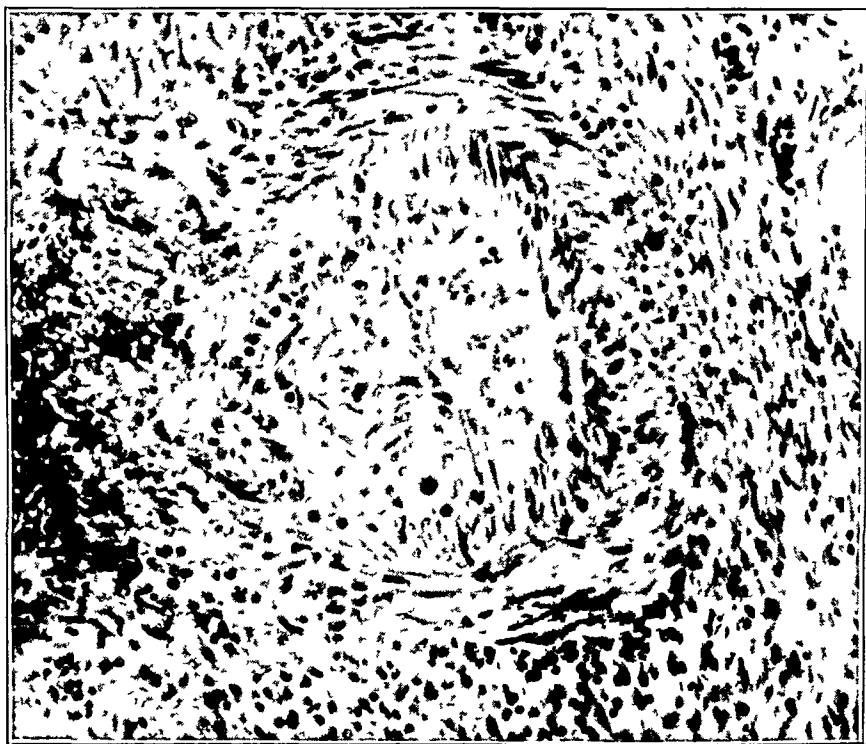


Fig 7—Syphilitic endarteritis (from same liver as shown in Figures 6 and 8) leading to occlusion of lumen and formation of infarct (gumma), one mitotic figure present

In the atrophied portions where there are no liver cells left the original lobular arrangement, much shrunken, can almost always be made out even if these parts have been stretched and pulled out of shape by excessive regeneration of liver cells in other parts. It is the only type of cirrhosis in which the condition occurs.

The early stage of this type of cirrhosis is often recognized clinically owing to the rapid decrease in the size of the liver, often to a half or even a third of the original volume. It is usually called acute yellow atrophy of the liver owing to its greatly diminished size and

to the yellow color of the regenerated parts acute red atrophy is the preferable term

The lesions in the two remaining types of cirrhosis are chronic in type and take years in which to produce their effects

Alcoholic Cirrhosis—The cell lesion is characteristic and consists of an acidophilic reticulum which forms in the liver cells around the nuclei, apparently from coalescence of granules. It stains intensely with eosin by the eosin-methylene blue method after fixation in Zenker's fluid. In time (months to years) the cells die and are removed by the digestive action of polymorphonuclear and endothelial leukocytes

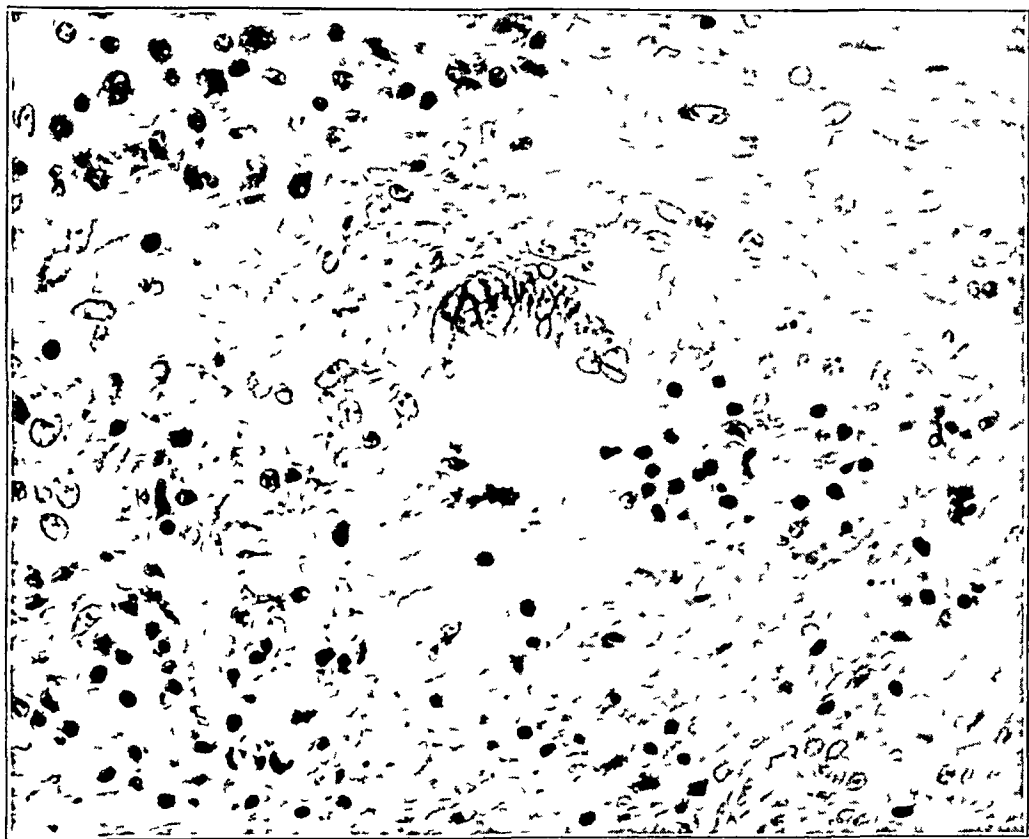


Fig 8—Foreign body giant cell at edge of gumma (same liver as shown in Figures 6 and 7)

Regeneration from other liver cells takes place diffusely and in foci. Where the cells die condensation of the stroma (sclerosis) occurs; where regeneration of liver cells takes place new stroma is formed, as in a tumor. In this way the amount of connective tissue in the liver is gradually increased as one crop of cells after another is killed off.

The gross picture of alcoholic cirrhosis is fairly characteristic. The external surface is finely to coarsely granular. The elevated portions represent the regenerated islands and groups of islands of liver cells, the depressed portions the contracted stroma. In the early stages



Fig 9—Typical syphilitic cirrhosis (hepar lobatum)

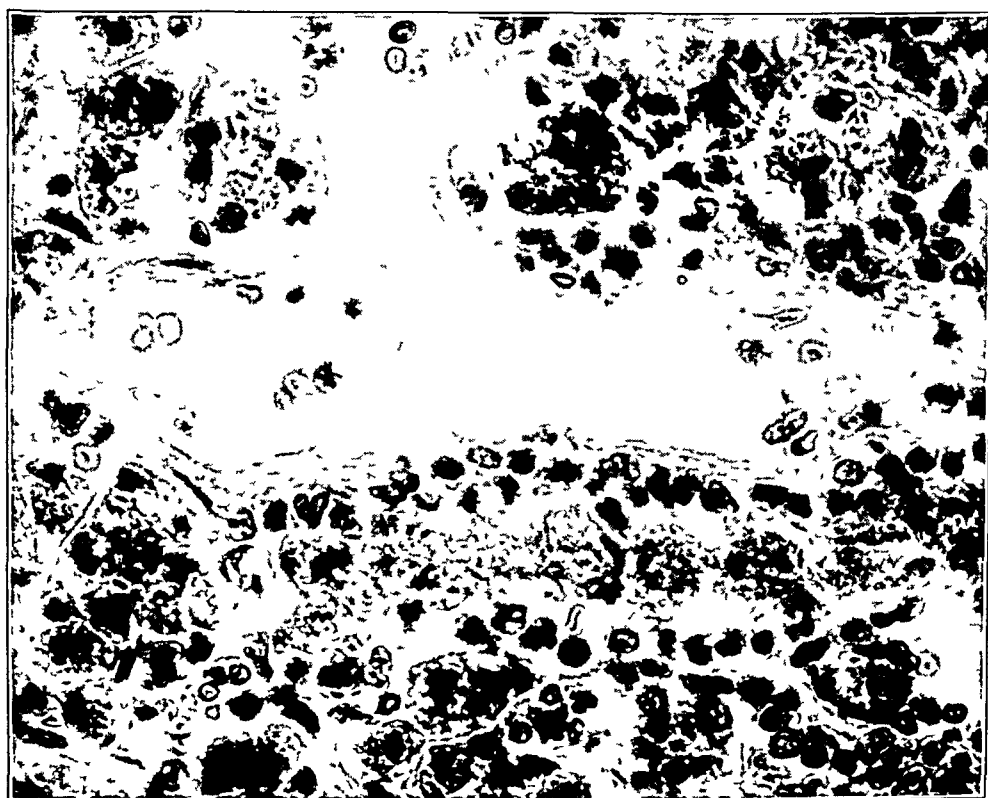


Fig 10—Necrosis of liver cells around hepatic vein, invasion by polymorpho nuclear and endothelial leukocytes

of the process the lesion is often complicated by marked fatty infiltration of the liver cells leading to great increase in the size of the liver

We came now to the fifth type of cirrhosis which forms the main subject of this paper. It is probably the slowest of the five types in developing, requiring apparently at least fifteen years

Pigment Cirrhosis, Hemochromatosis, Bronzed Diabetes—I shall speak of the macroscopic appearance of the liver first and then take up in detail the development of the lesion that leads to the gross picture. In many ways the liver, except for the rusty to dark brown color, resembles that seen in alcoholic cirrhosis. It may be larger or smaller

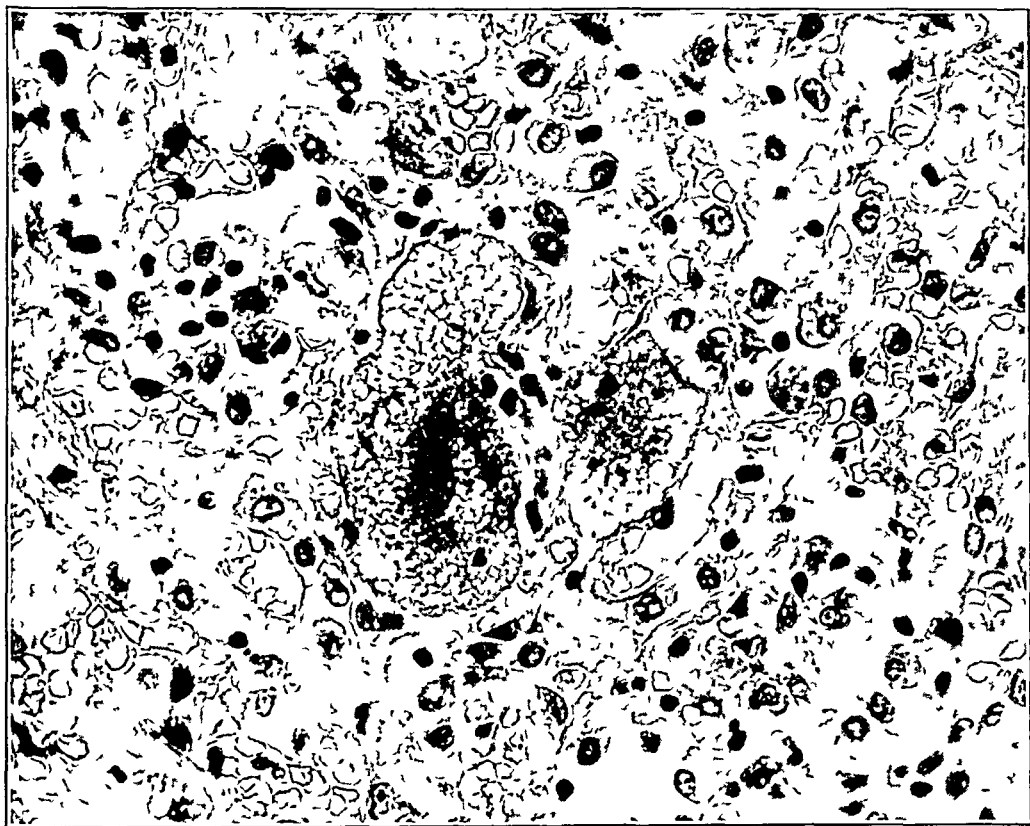


Fig. 11—Acute yellow atrophy, most of cells killed and removed by digestive action of leukocytes, a few liver cells left from which regeneration may take place

than normal according to the duration of the process¹ and its surface may be smooth to finely and coarsely granular depending also on the stage of the disease. It differs in one respect, however, from the alcoholic type—the lesion is rarely complicated by fatty infiltration, at least to any extent, and therefore the weight of the liver is never so great as it may be with the latter

1 Mills, E. S. Hemochromatosis with Special Reference to Its Frequency and to Its Occurrence in Women, *Arch Int Med* **34** 292 (Sept) 1924

Before proceeding to the histology of hemochromatosis I wish to mention certain effects that all five types of cirrhosis have in common. Contraction of the connective tissue in the foci of sclerosis leads to constriction of the blood vessels and of the bile ducts. Obstruction of the portal circulation causes distention and enlargement of the spleen, congestion of the gastro-intestinal tract and ascites. Dilatation of veins to effect a collateral circulation frequently leads to the production of varices in the esophageal plexus. Rupture of one of these dilated veins may result in sudden death from extensive hemorrhage into the stomach. Obstruction to the bile ducts leads to focal bile stasis within the liver and also to jaundice.



Fig 12—Cirrhosis following acute yellow atrophy, in the lobules where all the liver cells were killed no new formation of them takes place

THE HISTOLOGIC LESION OF HEMOCHROMATOSIS

From the pathologic point of view hemochromatosis began with von Recklinghausen. He gave the disease its name and observed that two yellow pigments were present in the lesions, hemosiderin, which gives the reactions for iron, and another which does not and which he called hemofuscin. He did not recognize or suggest a relationship between these two pigments although he believed them both to be derived from hemoglobin.

As the result of a careful study of a large series of cases of pigment cirrhosis and with better technical methods of fixing and staining at our command, Parker, Nye and I² were able to demonstrate that hemofuscin is the first pigment to be deposited in the liver and other cells and that in the course of time it is slowly changed to hemosiderin. The method of demonstrating the relationship is simple.

In pigment cirrhosis, as in the alcoholic type, there is a constant destruction of liver cells and an equally constant regeneration of them provided the process is at all active. The newly formed cells may be scattered diffusely among the older pigmented cells but usually occur



Fig. 13—Regeneration following central necrosis complicated by chronic passive congestion

in islands up to a millimeter or more in diameter. At first the new cells contain no pigment, then gradually granules of hemofuscin appear. They stain readily and intensely with basic aniline dyes, especially with a dilute solution of fuchsin in 50 per cent alcohol. In the course of time (months to years) these granules lose this staining property and give the reactions for iron.

² Mallory, F. B., Parker, Frederic, Jr., and Nye, R. N. *J. M. Res.* **42**: 461, 1921.

Hemofuscin deposited in fibroblasts and smooth muscle cells is usually changed with great slowness or not at all to hemosiderin. Consequently, this pigment can be found in these cells when, owing to the inactivity of the process, none is present in the parenchymatous cells of the liver or other organs because it has been changed to hemosiderin and gradually dissolved and eliminated.

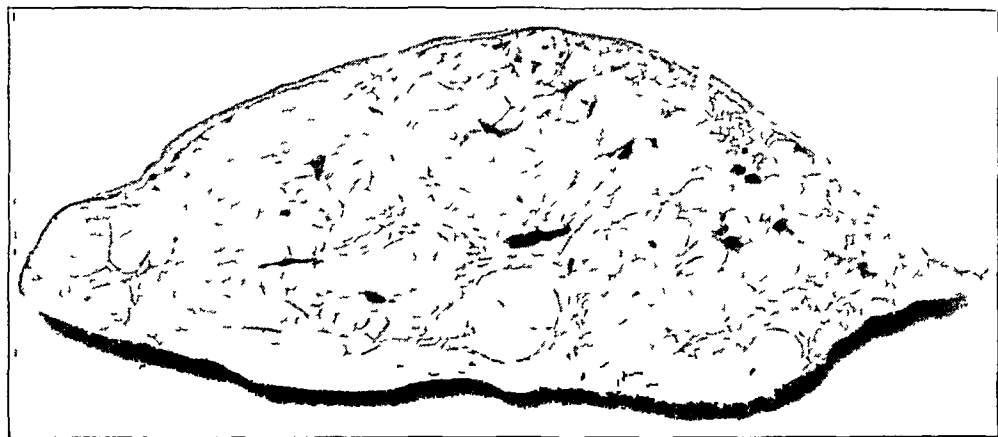


Fig 14—Cirrhosis of acute toxic origin containing islands of excessive regeneration, so-called adenomas



Fig 15—Cirrhosis of acute toxic origin in a girl, aged 15 years

The primary essential lesion of pigment cirrhosis may be stated, therefore, to be the deposit of a yellow pigment, hemofuscin, in the parenchymatous and other cells of the liver. Like the acidophilic reticulum of alcoholic cirrhosis this deposit of hemofuscin is the "finger print of crime" left by an injurious agent, the identity of which we wish to ascertain. In time hemofuscin changes to hemosiderin. The

accumulation of either pigment beyond a limited degree causes necrosis of certain parenchymatous cells. This starts regeneration and the process continues until the patient dies from the effects of the process itself or from secondary complications.

The cell changes in the pancreas are similar to those in the liver. deposit of pigment, necrosis of acinous and islet cells, regeneration. The physiologic result is the production eventually of diabetes mellitus. It is on account of this association of diabetes with pigmentation of the skin that the French have applied the term bronzed diabetes to hemochromatosis.

In the suprarenals the pigment is deposited chiefly in the outer layer of the cortex. It has been claimed that the normal pigments of the

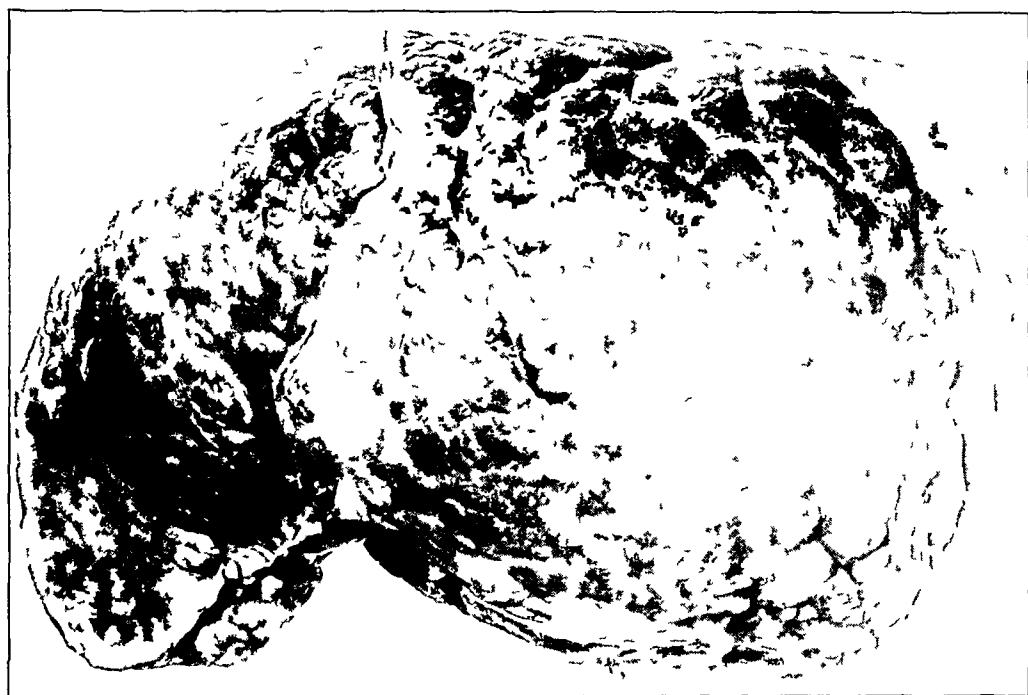


Fig. 16—Cirrhosis of acute toxic origin in a boy, aged 13 years

body, and especially that in the smooth muscle cells of the gastrointestinal tract, are increased in hemochromatosis. This would suggest that the lesion in the suprarenals might play some part in this increase were it not that proper staining of these smooth muscle cells shows the pigment to be hemofuscin except so far as it has been changed to hemosiderin.

The pigmentation of the skin is of great aid in rendering possible a positive diagnosis of hemochromatosis during life because the iron reactions can be made on sections of an excised piece.

The lesions in the kidneys are never marked, consisting chiefly of pigmentation of renal cells in the cortex. As the cells are killed off they desquamate, are washed out by the urine and are replaced by

regeneration There is no accumulation of pigment in endothelial leukocytes in the organ and no sclerosis

Pigment is deposited in cells all over the body, in the upper abdominal lymph nodes, in the heart, thyroid, brain, hypophysis, etc., but the effects are not serious because the patient dies as a result of the lesions in the liver and pancreas before they can develop in these other organs to any great degree

The essential lesion of hemochromatosis may be summed up, therefore, as the deposit of hemofuscin in parenchymatous and other cells of the liver, pancreas, suprarenals and other organs and tissues, the change

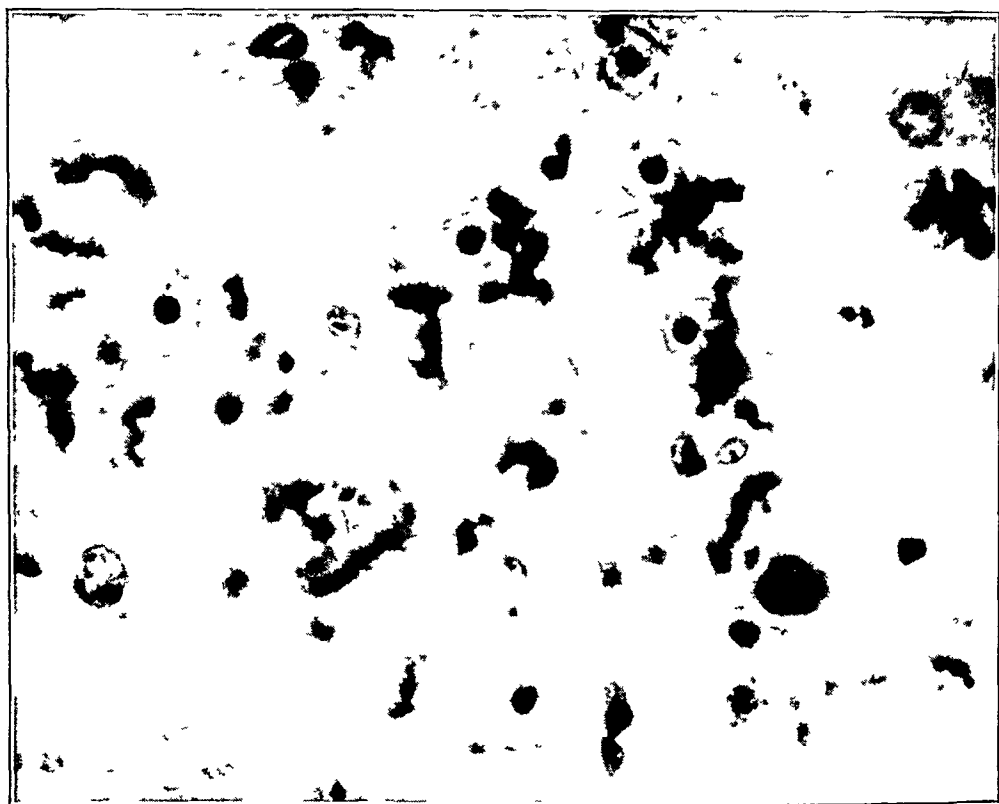


Fig 17—Liver cells showing hyaline reticulum characteristic of alcoholic cirrhosis

of hemofuscin to hemosiderin through the metabolic activity of these cells, necrosis and regeneration of some of the parenchymatous cells, especially in the liver and in the pancreas, condensation of the stroma when all the parenchymatous cells in certain areas have been destroyed, and the formation of new stroma in the islands of regeneration just as in a tumor The final result is sclerosis of the liver and pancreas with the consequent physiologic effects, ascites, jaundice and diabetes

CHRONIC POISONING WITH COPPER

Several years ago I found out that acetate of copper added to the food of rabbits produced pigment cirrhosis in from three to twelve

months according to the size of the dose. Eventually jaundice would develop and then the animals died quickly. One rabbit that was given small doses lived almost four years. The liver was finely granular, and deep olive brown owing to pigmentation and jaundice, but showed a number of small white granules of regenerated nonpigmented cells.

The pigment in the early lesions consists entirely of hemofuscin granules which stain intensely with basic fuchsin. Necrotic cells and mitotic figures are fairly numerous. The lesion is always most marked at the peripheries of the lobules and as the cells are killed off the pigment is taken up by endothelial leukocytes which tend to collect in the connective tissue around the portal vessels. Pigment also occurs in

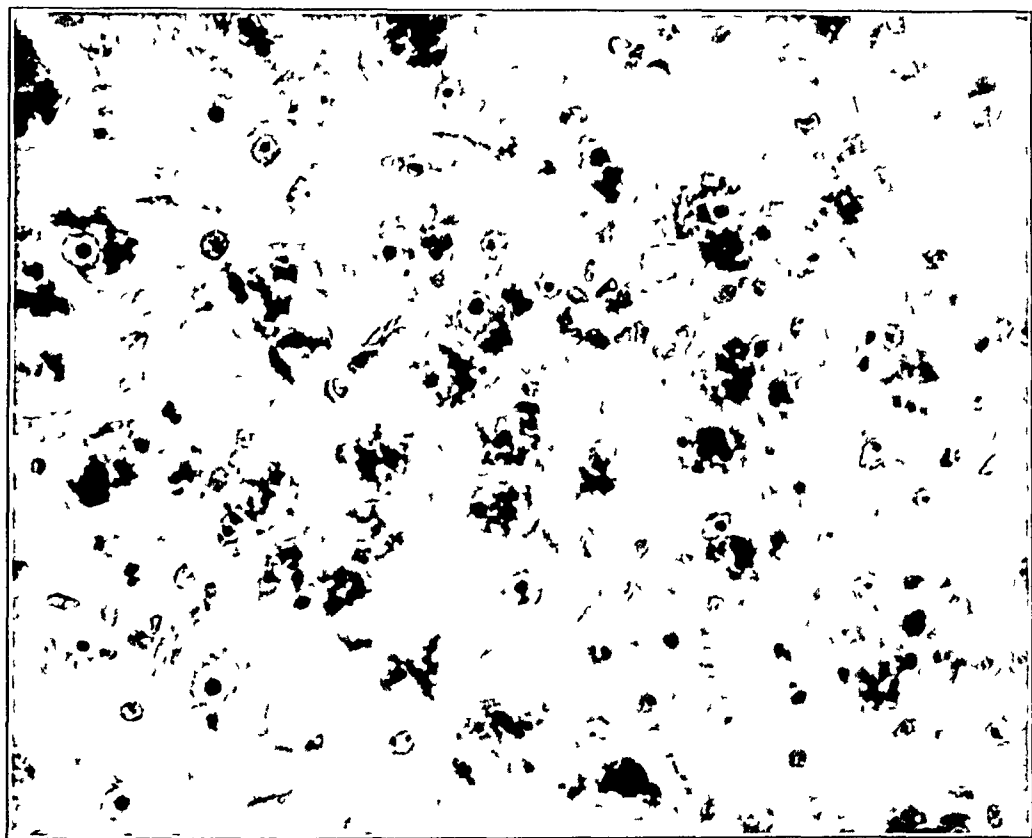


Fig. 18—Many liver cells containing hyaline reticulum; some have undergone necrosis and are being dissolved by endothelial leukocytes.

some of the renal cells and in the bone marrow, and in the animals that live longest is found in slight amount in the heart and in the pancreas.

Similar lesions can be produced in the monkey. In one small variety from South America the hemofuscin granules were changing to hemosiderin at the end of five and one-half months. In the rabbit the change is moderate even at the end of nearly four years.

The sheep was found very susceptible to copper poisoning, requiring no larger doses than the rabbit. The liver at the end of one year showed beginning cirrhosis, considerable hemofuscin and a slight amount of



Fig 19—External appearance of typical lobnail liver in alcoholic cirrhosis

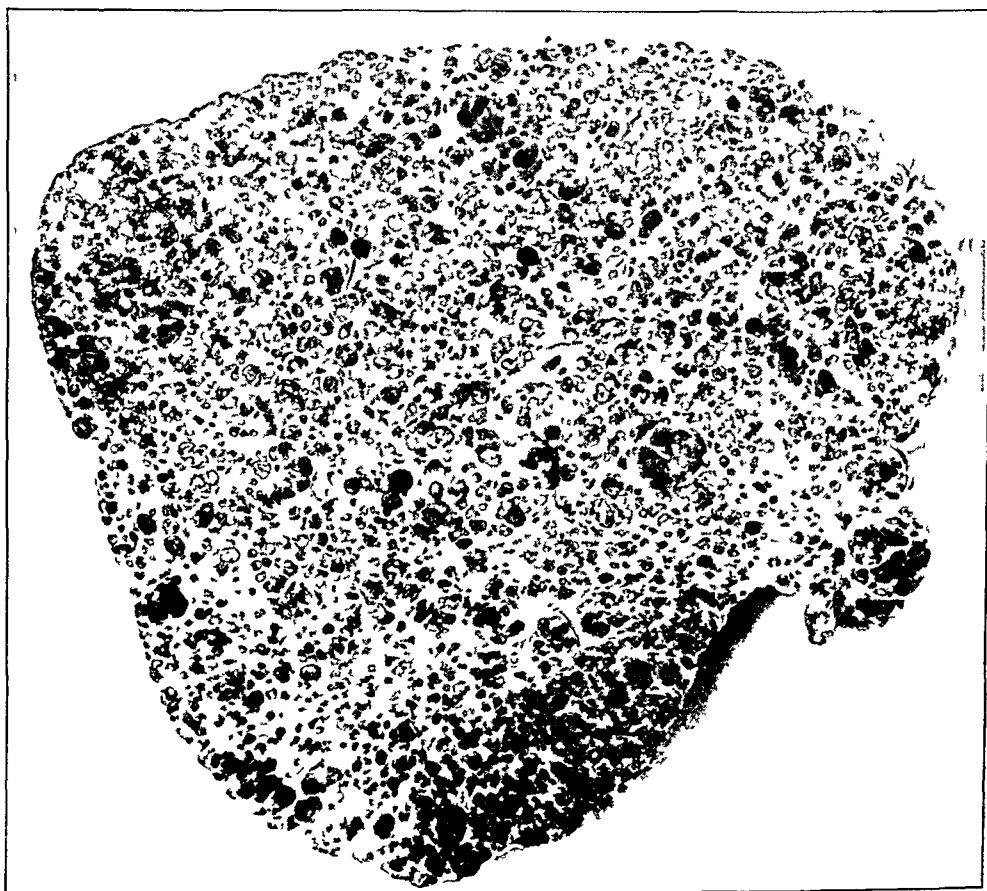


Fig 20—Section of liver shown in Figure 19

hemosiderin, but the animal died not from the liver lesion but from marked deposit of hemoglobin in the tubules of the kidney. Larger doses of copper produce the same condition in rabbits. It is evidence that copper must exert a hemolytic effect on red blood corpuscles.

So far as experiments have been carried out guinea-pigs do not seem to be injured by copper.

PATHOGENESIS OF HEMOCHROMATOSIS

The cause of hemochromatosis has always been a subject of great interest. A clinical study¹ of all the cases that had come to necropsy at the Boston City Hospital from 1897 to 1923 was made to see if

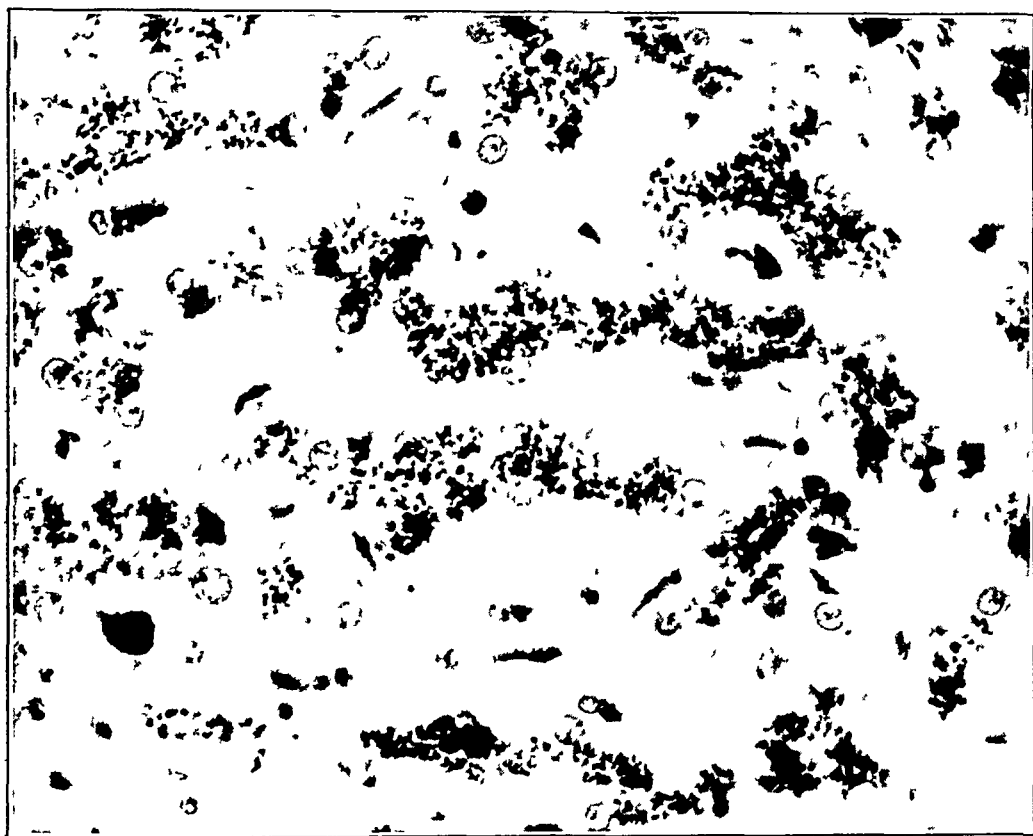


Fig 21 —Granules of hemosiderin in liver cells in pigment cirrhosis

they would throw any light on the etiology. It was found that the patients could be divided into three groups:

A Those who had indulged in alcohol to excess for many years

B Those who had worked at an occupation involving exposure to copper

C Those whose histories throw no light on a possible cause

These three groups will be discussed separately.

A *Alcohol*—Excessive use of alcohol has long been recognized as a possible cause of hemochromatosis. In this series of nineteen, seven

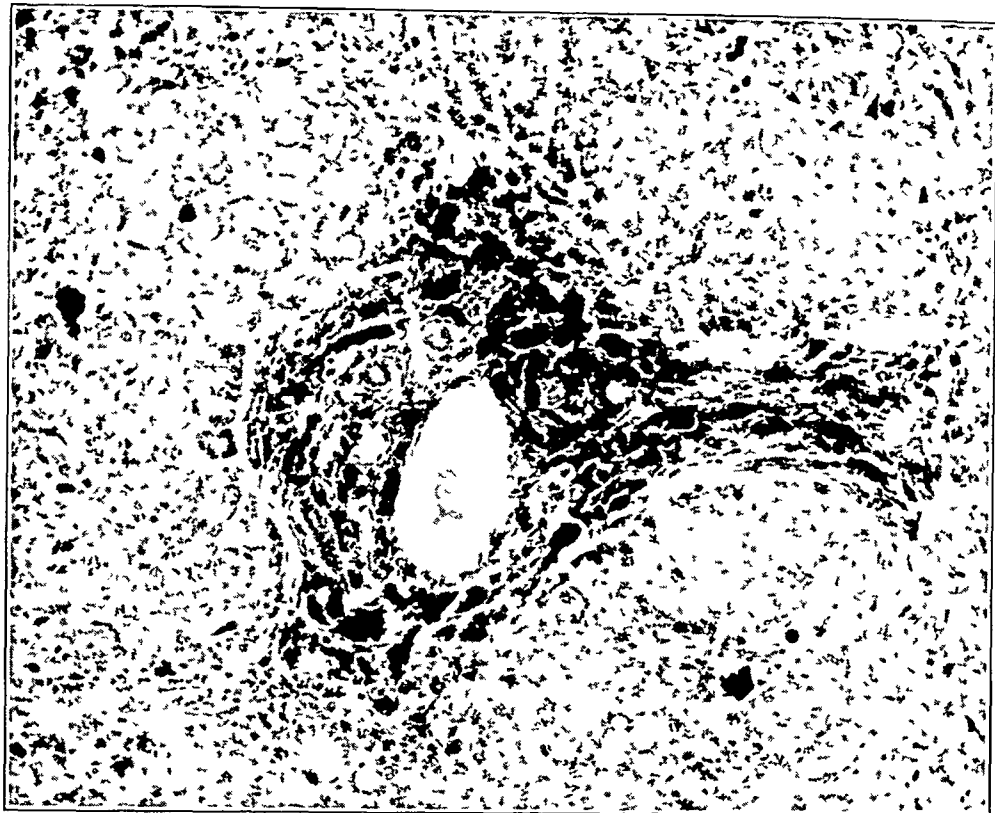


Fig 22—Granules of hemosiderin in liver cells and also in masses in endothelial leukocytes collected around portal vessels

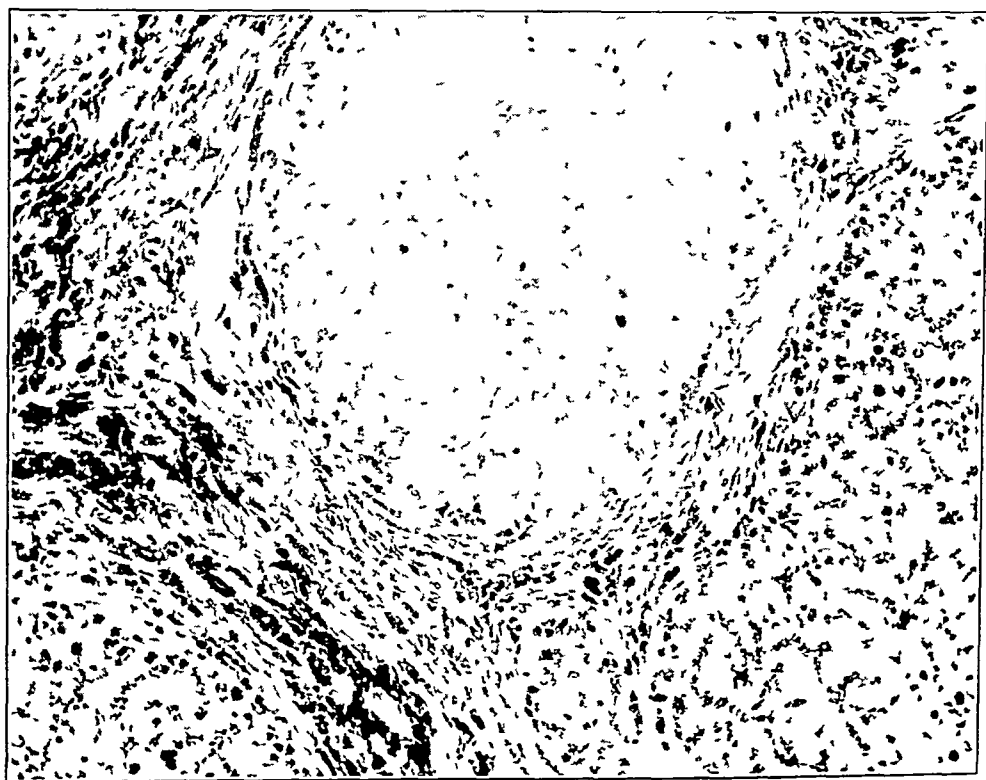


Fig 23—Pigment cirrhosis showing an island of regeneration in which the cells contain little pigment

at least belong in this group. A case with the most typical alcoholic history occurred at the Peter Bent Brigham Hospital and was placed at my disposal by the surgical service. A man had been a barkeeper for four years before prohibition went into effect. Then for six years he was a bootlegger and in addition ran a private still, making corn whisky. The worm in the condenser was pure copper. He entered the hospital for hemorrhoids. The surgical intern, Dr Harlan F Newton, formerly an intern with me, noticed that the patient's skin was pigmented, especially over the extremities. Examination of the urine showed the presence of sugar. Sections of an excised piece of

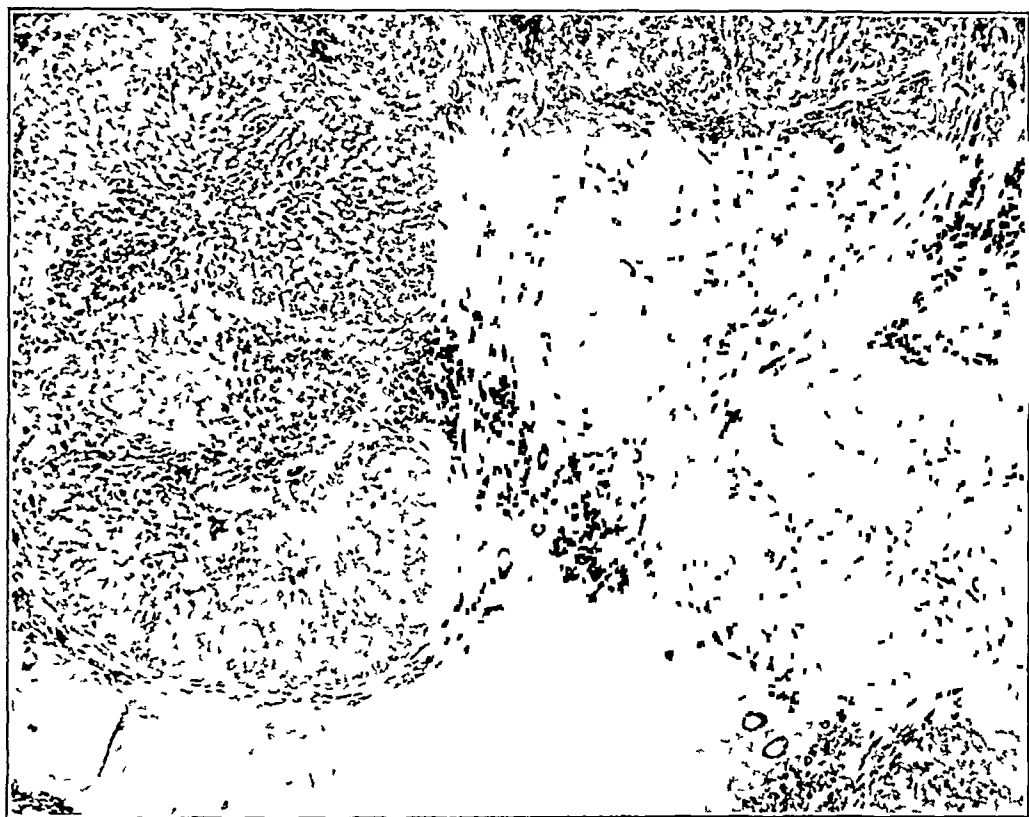


Fig. 24—Late stage of pigment cirrhosis

skin gave a marked iron reaction owing to a deposit of hemosiderin around the coil glands and also in fibroblasts and fat cells.

A series of eight distilled liquors examined for me by Dr Lawrence T Fairhall showed in seven from a trace to 10 mg of copper to the liter. The eighth contained 185 mg to the liter.

One of my former interns, now a surgeon, Dr Halsey B Loder, brought in a sample of home brew manufactured by a patient whom he had just tapped for ascites secondary to cirrhosis of the liver. The addition of a few drops of a 2 per cent solution of ferrocyanid of potassium caused a well marked reddish brown. Chemical examination showed the presence of 25.5 mg of copper to the liter. This test is

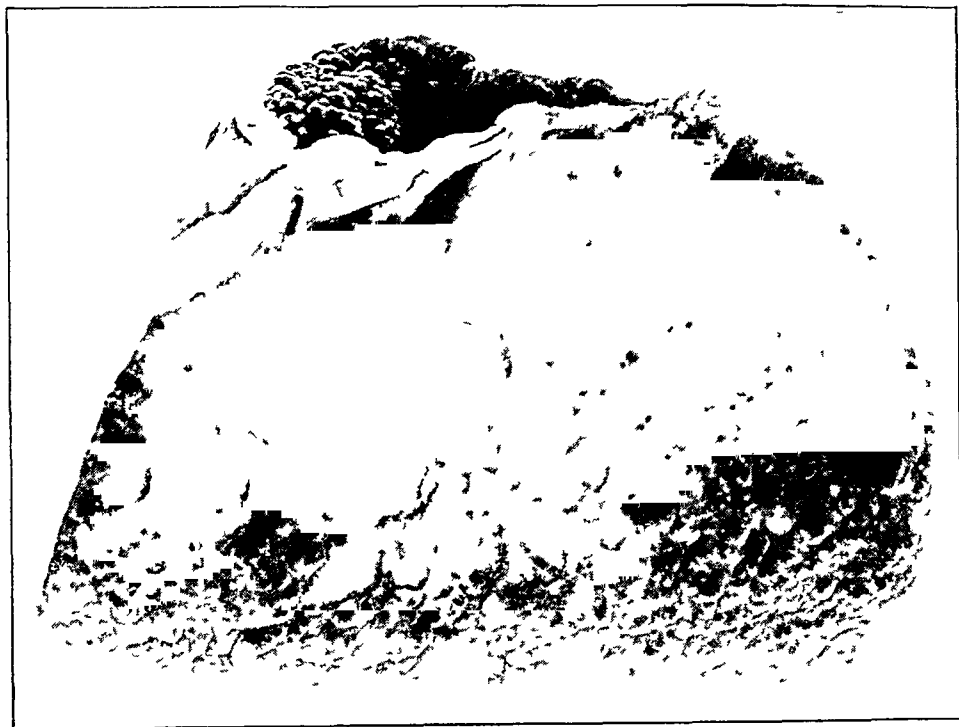


Fig 25—External appearance of liver of pigment cirrhosis

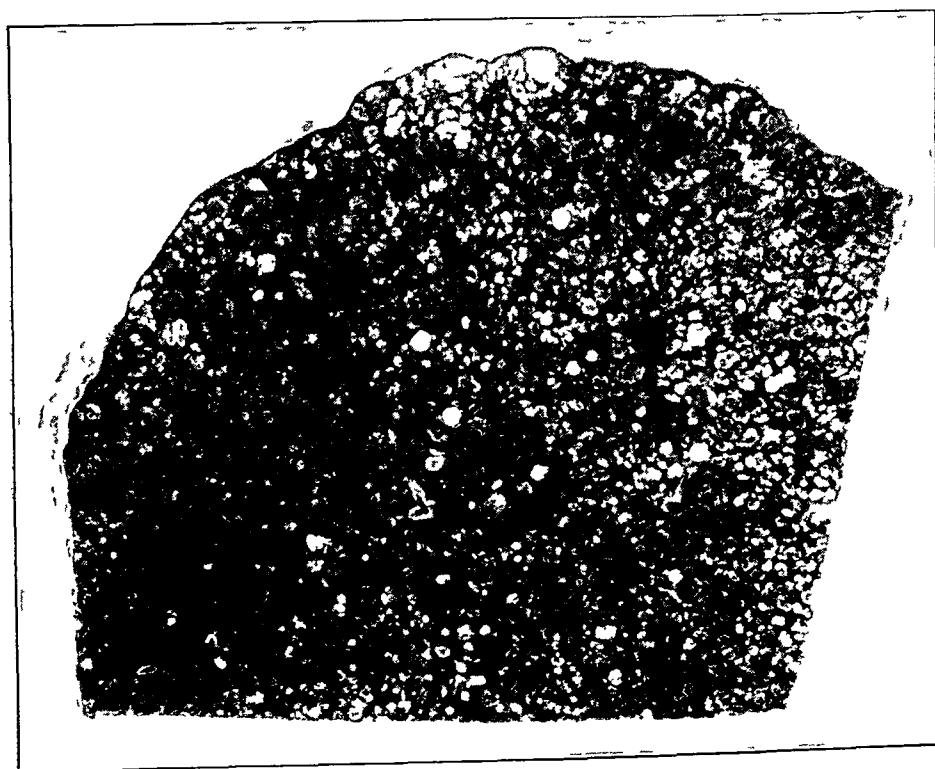


Fig 26—Cut surface of liver shown in Figure 25, the color of the recent islands of regeneration varies from white to gray

not so delicate as that with potassium xanthogenate, which yields a bright yellow color, but both work perfectly satisfactorily with specimens of liquor even when they are more or less colored. Using the first method, Herman C Lythgoe, director of the division of foods and drugs of the department of public health of Massachusetts, has tested 798 samples of "hooch" and found copper present from a trace up to 32 mg. to the liter in 10.8 per cent.

If a man were to drink a quart of whisky a day of the variety containing 185 mg. of copper to the liter (a not at all impossible feat) he would take into his system about 1 Gm. of copper a week, or 52 Gm.

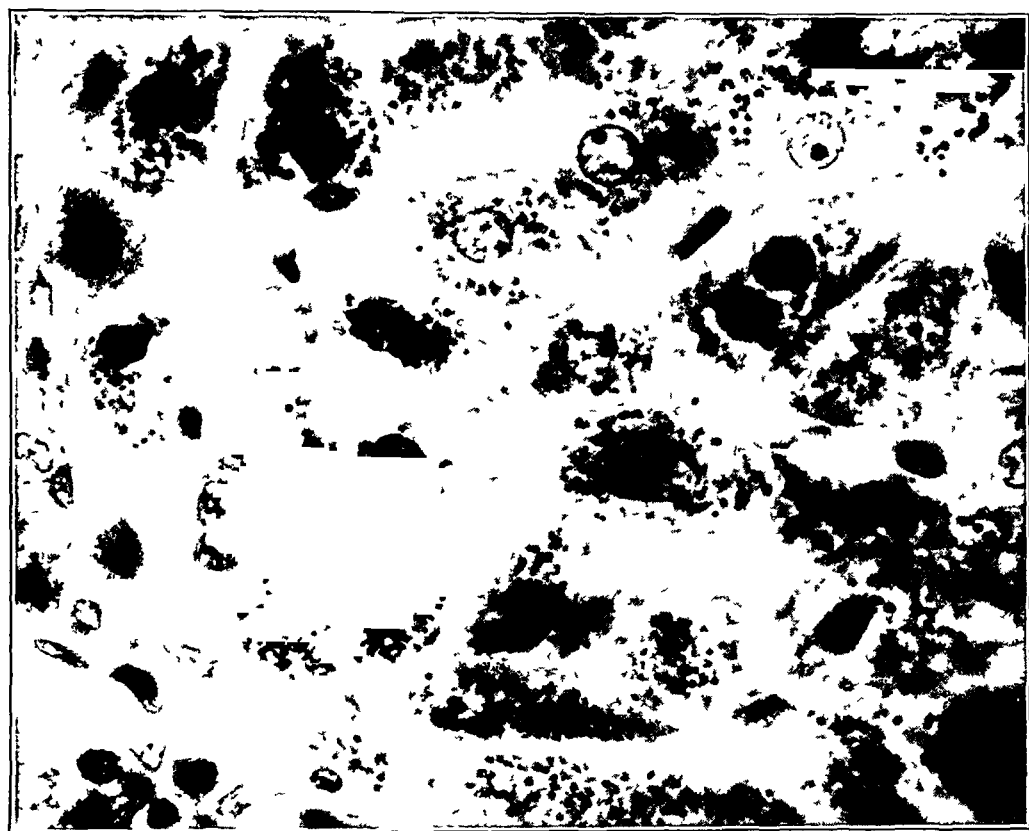


Fig. 27.—Granules of hemofuchsin in the liver cells and in endothelial leukocytes following poisoning with copper.

a year. It requires, according to all clinical evidence, at least ten and probably from fifteen to twenty-five years or more to produce the symptom complex known as hemochromatosis. In ten years he would have ingested over a pound (0.5 Kg.) of copper or 3 pounds (1.4 Kg.) of one of its salts. This amount would compare favorably, taking into consideration time and weight, with the amount of copper needed to produce pigment cirrhosis in the rabbit or sheep.

The natural inquiry is, How does the copper get into the liquor? It is easy to show that it is due to the action of organic acids in the mash distilling over with the alcohol and acting on the copper worm

of the condenser when that metal is used. A simple and quick way of testing the action of acids on copper is to shake a small amount (0.1 Gm.) of metallic copper in fine powder form in 10 cc. of a 1 per cent solution of any acid in question for fifteen minutes and then to filter. Some of the acids will color the solution bluish green in this time. The action of nitric acid is the most marked but citric acid comes close to it and then follow malic, lactic, acetic, tartaric, tannic and other acids. By precipitating all of the copper in solution by means of ferrocyanid of potassium an idea of the relative amounts dissolved by the different acids can be obtained.

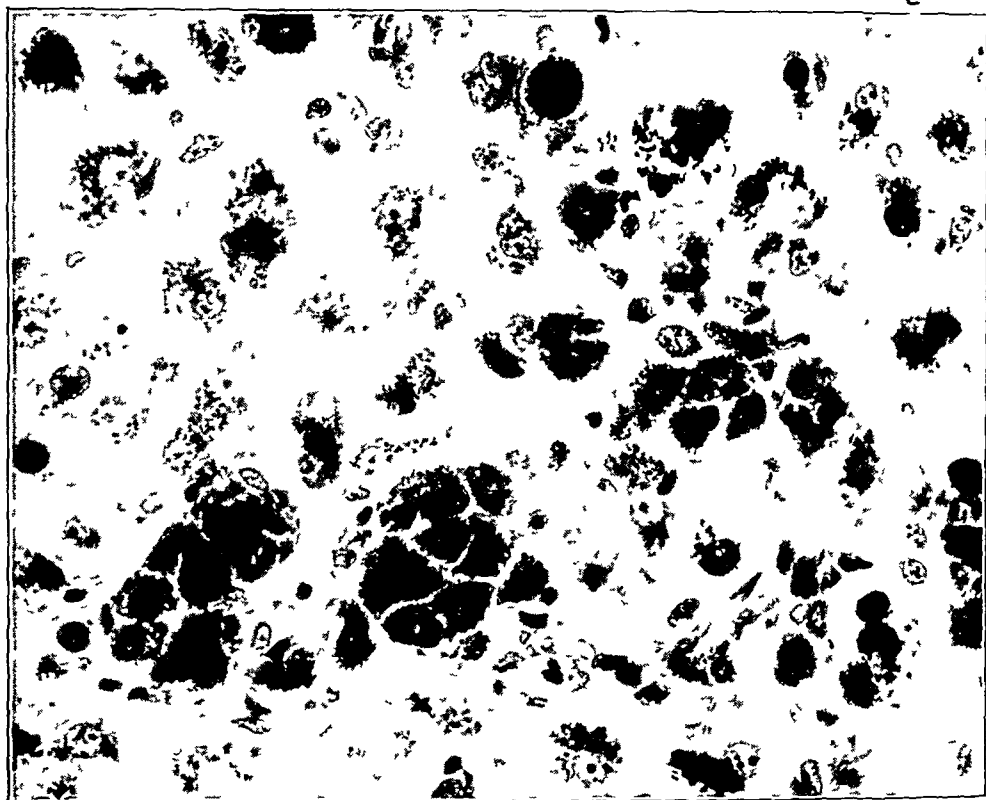


Fig. 28—Many endothelial leukocytes containing hemofuscin granules obtained from digesting necrotic liver cells containing them

B Occupation—Three of the nineteen patients had worked for from thirteen to thirty-eight years in foundries exposed to the dust from copper and brass. A fourth was a telephone lineman for twenty-three years, constantly handling, cutting and scraping copper wires.

The most typical illustration of the relation between occupation and disease was again furnished by the Peter Bent Brigham Hospital through the kindness of Dr. Henry A. Christian. The patient had worked for fourteen years in a shop "milling and turning copper and brass."

Three men who came to necropsy at the Boston City Hospital had worked for from six to forty-five years in brass foundries. Although no cirrhosis was present all three showed the two characteristic pigments, hemofuscin and hemosiderin, in moderate amounts in the liver and in the pancreas, and skin excised during life from two who showed slight pigmentation gave a moderate reaction.

The question of what would become of copper dust inhaled or swallowed led to experimental work which at first sight seemed foolish to attempt. The result of it, however, was to find that metallic copper in fine powder form injected in suspension in water or gelatin solution

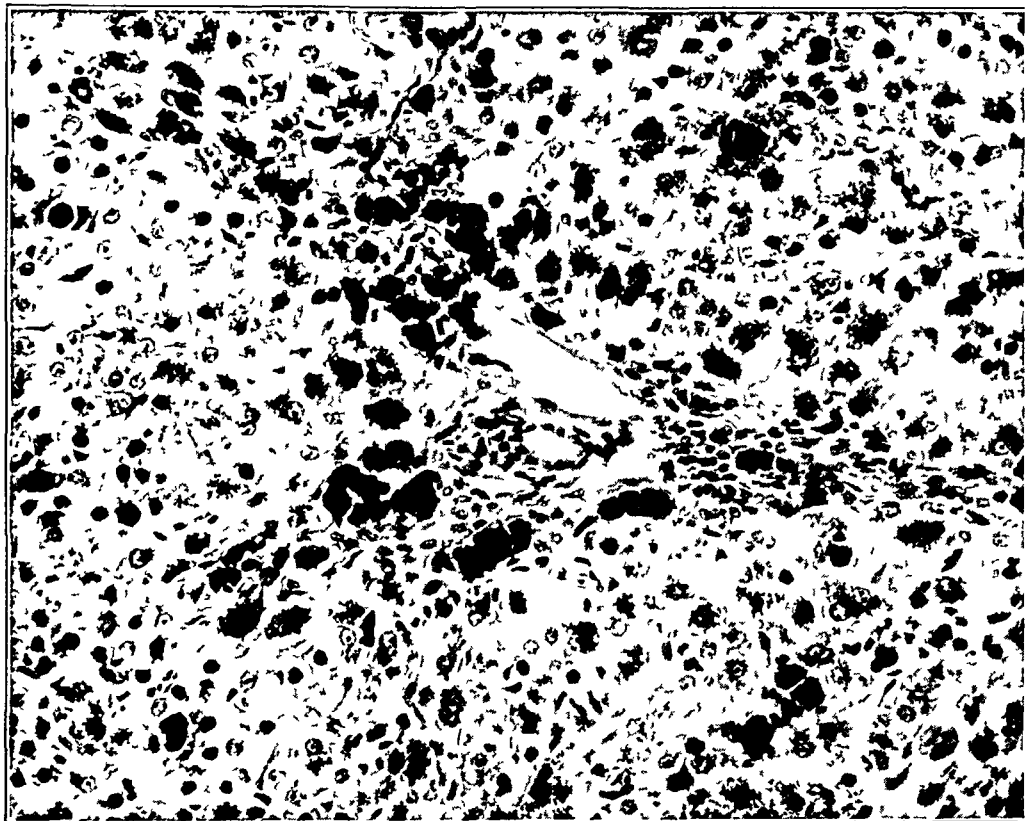


Fig 29 —Early stage of copper cirrhosis

was readily dissolved in the body no matter how it obtained entrance, whether through the lungs or the stomach, injected into the blood stream or subcutaneously. It seems most probable, judging from the recent work of Rous, that the copper is dissolved owing to the acid reaction of the endothelial leukocytes which quickly take up the particles of metal. When powdered metallic copper was injected into the lung the solution formed was so strong that it caused necrosis of the tissue. When injected subcutaneously the surrounding muscle fibers were killed and lime salts were deposited in them within a few days. The local inflammatory reaction was always well marked.

The general effect of the copper salt formed from the metal was the same as obtained by injecting or feeding acetate of copper. Hemofuscin was deposited in the liver and in time gave rise to pigment cirrhosis. If too much copper was administered hemoglobinuria occurred, indicating excessive destruction of the red blood corpuscles.

C Cause Unknown—In more than a third of the cases of hemochromatosis no evident source of chronic poisoning with copper was apparent. It was necessary, therefore, to consider the possibility of other sources than those connected with alcohol and occupation.

Ten cases occurring in one year gave opportunity for chemical examination of the liver and other organs for copper. In one instance

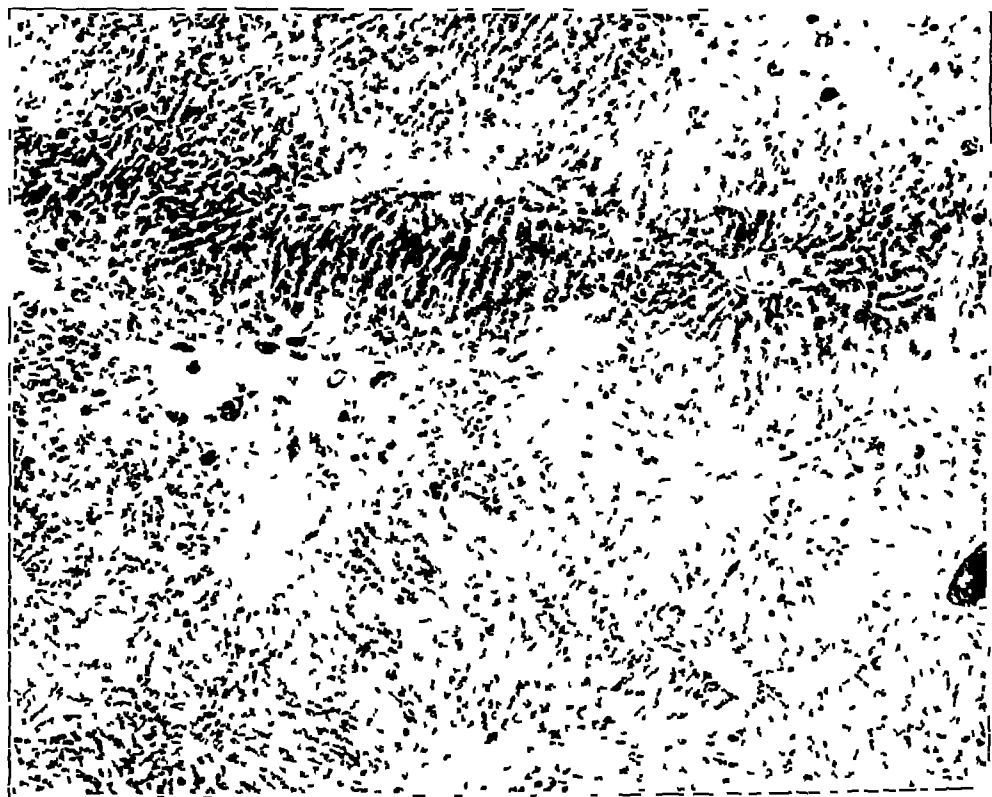


Fig 30—Late stage of copper cirrhosis much sclerosis present

as much as 20 mg was obtained from a kilogram of tissue and less amounts in others, but a series of controls yielded results almost as high, indicating that we must be constantly exposed to the danger of ingestion of copper.

One of the patients in this group had worked for eighteen years in a cannery cooking fruits in copper kettles. Ingestion of a sufficient quantity of canned fruits containing copper might in time produce pigment cirrhosis. That is a source of poisoning to which we are all exposed. Before making any claims for this possibility, however, it would be necessary to examine chemically a series of acid fruits that

had been cooked in copper kettles to find out if they contained any copper and if so how much

Apple butter is much used in some parts of the country and is commonly made in copper kettles. The malic acid in it readily attacks copper. This would seem, therefore, to be another source for copper poisoning. The same is true of copper tea and coffee pots, as copper is dissolved to a slight extent by the tannic acid contained in tea and coffee.

If copper powder is shaken in melted lard for fifteen minutes and then filtered out the lard will be found to be colored blue green owing to the formation of copper oleate. The other fatty acids produce the same effect.

Hess³ has found that milk pasteurized by running over copper pipes may contain as high as 2 mg of copper to the liter, and that this amount interferes with the action of vitamin C so that scurvy may be produced.

Cocktail shakers are usually made of copper or brass and lined with silver or tin. When the latter metals are worn or dissolved off, the acids, for example citric, in the ingredients readily attack the copper. One Boston physician informed me recently that he was now mixing cocktails in two glasses. The shakers used at soda water fountains for mixing lemonades are usually made of copper.

The brass water pipes in Brookline, where I live, are so eroded after from fifteen to eighteen years that a pin can be thrust through them almost anywhere. The amount of copper obtainable from water running through such pipes must be minute but it represents a possible though unlikely source of danger.

The examples cited here show that we are constantly exposed to the action of copper. The fact that our organs on chemical examination yield a certain amount of it does not mean that copper is a normal and necessary constituent of the body but that we cannot get away from it. This does not mean, of course, that we are all suffering from copper poisoning. It seems perfectly evident that we can handle a certain amount of the metal without danger, perhaps from 5 to 10 mg a day, possibly more. The only visible effect may be the presence of a little hemofuscin in fibroblasts in the liver and some of the other organs where it cannot be transformed into hemosiderin and then be gradually dissolved and removed. If, however, the amount absorbed exceeds a certain definite limit the danger of pigmentation of the liver and pancreas is evident.

3 Hess, A. F., and Weinstock, Mildred. Catalytic Action of Minute Amounts of Copper in Destruction of Antiscorbutic Vitamin in Milk, *J. A. M. A.* **82** 952-956 (March 22) 1924.

It is quite possible that susceptibility may play an important part. Some rabbits succumb much more quickly than others. Sheep are very sensitive while guinea-pigs seem to be almost or entirely immune.

Apparently the chief action of copper absorbed into the body is to cause hemolysis of the red blood corpuscles so that the hemoglobin is set free in the circulation. Part of the hemoglobin is eliminated through the kidneys but any excess is deposited in a changed condition as hemofuscin in the liver and later in some of the other organs.

The hemofuscin is not a compound of copper with hemoglobin but an intermediate product between hemoglobin and hemosiderin. This can be demonstrated by repeated injections of hemoglobin, obtained by the ether method from rabbit's blood, into another rabbit. In a few days hemofuscin will begin to be deposited in the liver. Hemofuscin is also formed around old hemorrhages where hemoglobin is being transformed by endothelial leukocytes and fibroblasts into hemosiderin.

CONCLUSIONS

Evidence is slowly but steadily accumulating in favor of the view that chronic poisoning with copper causes the symptom complex known under the different names of hemochromatosis, bronzed diabetes and pigment cirrhosis.

Copper is an exceedingly useful and indispensable metal in many ways but it should not be employed where it may come in contact with foods or drinks, especially if they contain acids of any sort, because it is so readily dissolved by many of them. This would exclude its use for cooking utensils of any sort, for shakers of cocktails and acid drinks, and for the worms of the condensers in stills.

Its use in pipes for drinking water and for hot water heaters is probably without danger.

PRIMARY CARCINOMA OF THE LIVER*

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In the last ten or fifteen years a voluminous literature has been accumulating with regard to the effect of chronic irritations and destructive processes on the development of cancer. The relation between normal, hyperplastic, adenomatous and cancerous changes is still extremely obscure, but it is highly probable that there is a definite connecting link. Where the boundary line between a benign and a malignant cell can be drawn, and what agencies or conditions are responsible for the change from the one to the other, are questions on which diverse opinions are held. The work of MacCarty¹ and Broders² on cellular pathology and on the factors influencing malignancy are important. Primary carcinoma of the liver occupies a unique position among malignant tumors, not only on account of its rarity but also from its habits of growth and spread, and from its frequent association with cirrhosis. In studying the five cases reported here we have paid particular attention to the cirrhotic element, and to its probable relationship to the accompanying malignant change.

A complete review of the literature would be impossible, for this the papers of Eggel,³ Goldzieher and von Bókay,⁴ Winternitz,⁵ and others should be consulted. It will suffice to state that our knowledge really begins with the work of Sabourin⁶ in 1881 and of Hanot and Gilbert⁷ in 1888. Prior to that time primary carcinoma was considered much more common than secondary carcinoma and as a result the

* Work done in the section on pathologic anatomy, Mayo Clinic

1 MacCarty, W C. A Biological Conception of Neoplasia. Its Terminology and Clinical Significance, *Am J M Sc* **157** 657-674 (May) 1919

2 Broders, A C. Cancer's Self-Control, *M J & Record* **121** 133-135 (Feb 4) 1925

3 Eggel, H. Ueber das primare Carcinom der Leber, *Beitr z path Anat u z allg Path* **30** 506-604, 1901

4 Goldzieher, M., and von Bokay, Z. Der primare Leberkrebs, *Virchows Arch f path Anat* **203** 75-131, 1911

5 Winternitz, M C. Primary Carcinoma of the Liver, *Rep Johns Hopkins Hosp* **17** 148-184, 1916

6 Sabourin, Charles. Contribution a l'etude des lesions due parenchyme hepatique dans la cirrhose, *essai sur l'adénome du foie*, Paris, 1881, No 39

7 Hanot, V C, and Gilbert, A. Etudes sur les maladies du foie cancer (epitheliome), sarcome, melanomes, kystes non parasitaires, angiomes, Paris, Asselin and Houzeau, 1888

statistics were confused. Despite Virchow's warning that before a diagnosis of primary carcinoma could be made a most careful search of the eye, breast and gastro-intestinal tract should be carried out for a primary focus, series of cases were reported which were later considered entirely unacceptable. Thus of the nineteen cases of Frerichs,⁸ von Paul⁹ and Lancereaux,¹⁰ von Hanseemann¹¹ rejected all but two. He also demonstrated thoroughly that the incidence was low in comparison with that of secondary growths, by finding four cases in 258 in marked contrast to Leichtenstern's¹² seventy-two cases of primary carcinoma in 430 of both types.

In Hanot and Gilbert's series three gross types were recognized, "cancer massif," "cancer nodulaire" and "cancer avec cirrhose," with a further microscopic division into "cancer alvéolaire" and "cancer trabéculaire." Eggel, in an examination of 164 cases, came to the conclusion that this classification was unsatisfactory, especially with regard to "cancer avec cirrhose." Cirrhosis was found to be present in all types so that a separate class was not justified. He used a gross classification of massive, nodular and diffuse carcinoma, and to this we adhere. Yamagiwa¹³ dispensed with the rather cumbersome carcinoma adenomatosum, or "alvéolaire," and carcinoma solidum, or "trabéculaire," and substituted the term hepatoma for carcinoma of the liver cells and cholangioma for carcinoma of the bile ducts. By carcinoma of the bile ducts we mean only those arising from the smallest bile canaliculi and not those from other parts of the biliary apparatus. Although hepatoma was used originally by Sabouin to describe the condition of nodular hyperplasia, which he considered a transitional stage between adenoma and carcinoma, subsequent writers, following Yamagiwa, have appropriated it as a term for primary carcinoma of the hepatic cells. The French school as represented by Brulé¹⁴ still adheres to the classification and conceptions of Hanot and Gilbert, but the consensus of opinion elsewhere is that Eggel's three groups are the most satisfactory.

REPORT OF CASES

CASE 1—A man, aged 44, was admitted to the clinic, Nov. 13, 1914, complaining of pain in the lower part of the abdomen. Two weeks before admission, while he was at work, he had felt a cramplike pain around the umbilicus. His

8 Frerichs, quoted by von Hanseemann, D. Ueber den primären Krebs der Leber, Berl. klin. Wchnschr. **27** 353-356, 1890.

9 Von Paul, quoted by von Hanseemann (Footnote 8).

10 Lancereaux, quoted by von Hanseemann (Footnote 8).

11 Von Hanseemann (Footnote 8).

12 Leichtenstern, quoted by Eggel (Footnote 3).

13 Yamagiwa, K. Zur Kenntnis des primären parenchymatösen Leberkarzinoms ("Hepatoma"), Virchows Arch. f. path. Anat. **206** 437-467, 1911.

14 Brulé, M., in Castaigne, J. Traité de pathologie médicale de thérapeutique appliquée, Paris, **12** 383, 1923.

appetite was not affected, but he vomited occasionally after working. A few days before admission, he had noticed that the abdomen was swelling and that the pain, which was more severe after defecation, had shifted to the right upper quadrant. During the last year he had lost 25 pounds (11.3 Kg) in weight.

Examination showed mild jaundice; the abdomen was tympanitic and tender below the right costal margin, but dull in the flanks owing to fluid. The spleen and the liver were both slightly enlarged, the liver extending 7 cm below the right costal margin. On exploratory laparotomy the peritoneal cavity was found to be filled with blood stained fluid and the liver to be enlarged and nodular. A diagnosis of carcinoma of the liver was made and the abdomen was closed without further procedure. The patient gradually became weaker and died on the fifth day.

Necropsy was performed fourteen hours after death. Cirrhosis of the liver, primary carcinoma of the liver, chronic splenitis, ascites, slight bronzing of the skin, chronic catarrhal cholecystitis and dilatation of the bile ducts, chronic congestion of the abdominal viscera, myocardial degeneration and pulmonary edema were found.

The skin and mucous membranes were slightly yellow and the face and neck were dark and bronzed. There were several hundred cubic centimeters of blood tinged fluid in the peritoneal cavity. The spleen was enlarged, measuring 18 by 12 cm. The pancreas was firmer than normal, the head being slightly enlarged. The lymph nodes at the hilum of the liver were enlarged and soft. The gallbladder was dilated and contained about 15 cc of thick, mucoid bile, but there were no lesions of the mucosa. The extrahepatic bile ducts were dilated (Grade 3) but patent throughout. The portal and the mesenteric vessels were dilated. The liver was enlarged and extended 7 cm below the costal margin. The whole surface was coarsely nodular, the largest nodule being situated in the right lobe. The nodules varied in diameter from a few millimeters to 5 cm. The capsule was thickened, opaque and yellowish white without adhesions to the surrounding structures. On section the entire right lobe appeared to be replaced by nodules, each one being surrounded by a thin fibrous capsule. Many of them were grouped in masses and were surrounded by a thicker capsule of compressed liver tissue. In the left lobe they tended to be more discrete. Most of them were cream colored, but the color varied from light brown to greenish red. The consistency near the periphery was firm, but in the center it was soft and putty-like. The remainder was dark green, compressed, scarred and coarsely granular. The fibrous tissue trabeculae produced a network arrangement throughout the entire section. A main branch of the portal vein was completely filled with tumorous tissue resembling the larger nodules, and there were a few small blood clots around the mass, adherent to the main wall. A few of the smaller portal branches appeared to be plugged with the same tissue, but the hepatic veins were free.

Sections for histologic examination were taken from various portions of the liver. The normal architecture was in many places profoundly altered by the pressure of large and small nodules scattered throughout so that sections from any portion must necessarily include these areas. The liver tissue was everywhere involved in a marked cirrhotic process, irregularly distributed, but most abundant in the region of the periportal spaces. Here and there large and small bands of fibrous tissue extending from the periportal spaces surrounded areas of liver tissue, which had for the most part lost its radiate arrangement and central veins. In other situations there were huge scars altogether devoid of liver cells. The fibrosis was more pronounced in sections in which the tumor compressed the cells. The connective tissue in the periportal spaces was rather more dense around the vessels than around the bile ducts, and was infiltrated with numerous small tortuous bile ducts, while lymphocytes, diffusely scattered in some areas and massed together in others, formed a prominent feature. They did not, however, extend into the hepatic sinusoids. The

nodules so enclosed appeared adenomatous, with the cells at the periphery clean-cut, convex and more intensely stained with hematoxylin than the central cells. It was evident that hyperplastic processes were in progress in this situation. Fatty degeneration, evidenced by vacuolation and coarse granulation, was more marked in the center of these areas. Inspissated bile was present in the bile canaliculi, and the cells themselves contained bile pigment. It was particularly well marked in the connective tissue spaces. The tumorous nodules consisted of large masses of polygonal, rectangular and oval cells with a more or less trabecular arrangement. Throughout their substance were bands of connective tissue well shown by the van Gieson stain, forming a network in which the cell groups lay. For the most part, the cells lay within blood vessels which could be recognized by their intimal and muscular layers. The expansion of these vessels had produced atrophy and destruction of the surrounding liver cells. Many areas showed necrosis of the walls of the blood vessels with invasion of the hepatic parenchyma by tumor cells. Although at first sight there appeared to be a transition between normal and abnormal cells in these situations, a close examination failed to reveal any such change, and a definite demarcation between the two was always apparent. The abnormal cells varied greatly in size and appearance, but for the most part they bore a general relationship to the normal liver cell. The cytoplasm was rather granular and showed fatty changes, but the nuclei stained deeply and were hyperchromatic and often pyknotic. Mitosis was frequent and giant cell forms were abundant. Bile pigment could not be distinguished within the cells, but it appeared in the intercellular spaces and around the periphery in the connective tissue. Where the tumorous emboli had retracted from the vessel wall, the endothelium adhered to the surface. The cells extended into small branches of the portal vessels and then expanded into nodular masses filling every crevice of the vascular spaces. The malignant tissue was well preserved and distinguishable from the normal parenchyma by its more intense staining reaction, prominent capillary stroma, encapsulation by extremely dense fibrous tissue, and branchlike character where tumor thrombosis had occurred. Although grossly the hilum nodes were enlarged and soft, no tumorous tissue was discovered microscopically. This case was undoubtedly a primary carcinoma of the liver cells or hepatoma of the diffuse form.

CASE 2—A man, aged 63, was admitted to the clinic, June 23, 1923, complaining of swelling of the abdomen and pain at the right costal margin. He had suffered from gastric disturbances periodically for three years, but had not been incapacitated until four months before his examination when he began to have frequent attacks of severe pain in the right upper quadrant associated with bloating, nausea and more recently vomiting of dark brown material. One month later the pain became more severe, and a tender mass could be palpated below the right costal margin extending across the epigastrium just above the umbilicus. The patient had lost 15 pounds (6.8 Kg.) during the previous four months. He had noticed an occasional dark stool.

On examination the skin and mucous membranes were slightly jaundiced, and there was slight bronzing of the face and neck. The abdomen was distended and there was shifting dullness in both flanks. A mass was palpable across the epigastrium. The legs were slightly edematous. The blood was chemically normal.

Necropsy, performed three and one-half hours after death, revealed primary carcinoma of the liver with extension to the portal and hepatic veins, inferior vena cava, right auricle and branches of the pulmonary artery, metastasis to the lungs, cirrhosis of the liver with adenomas, ascites, old healed pulmonary tuberculosis with tuberculous pleuritis and splenitis.

The skin was moderately icteric and slightly bronzed over the face and neck. The abdomen was distended. The peritoneal cavity contained approximately 3,000 cc. of blood tinged fluid. The lower margin of the liver extended

8 cm below the costal margin. The gallbladder was normal. Numerous small, yellowish white nodules, measuring from 3 mm to 1 cm in diameter, projected through the pleura of both lungs. On section these were yellowish white and seminecrotic. The main branches of the pulmonary artery were free from emboli, but masses of yellowish white, tumorous tissue extended from the right auricle down into the inferior vena cava.

The liver was extremely irregular and mostly replaced by numerous yellowish white nodules which were plainly seen beneath its capsule. The liver tissue had been displaced between the capsule and the nodules. On section the greatest portion of the clay colored tissue was seen to consist of one mass, which involved approximately four-fifths of the right lobe. It was quite homogeneous, but the outer, lower and central portions near the hilum of the liver were divided by compressed fibrous tissue and remnants of liver into small, irregular, pasty nodules from 1 to 8 mm in diameter. In the upper part of the largest mass was a circumscribed area, measuring 4 cm in diameter, which consisted of reddish brown necrotic material studded by numerous small hemorrhages. On the left side near the hilum the tumor had invaded the portal vein and occluded it completely. This plug filled all the branches of the right lobe of the liver but only extended for a short distance into the branches of the left lobe. The inferior vena cava was likewise occluded by a mass which projected into it from the hepatic veins below. The lower one fifth of the right lobe was almost free from nodules, and was markedly compressed and congested. The liver tissue here was dark brown and divided by prominent irregular bands of fibrous tissue, which gave it a coarsely granular appearance. The left lobe of the liver was small and had the same granular structure.

Representative sections were taken from various portions of the liver for microscopic examination. Sections from the left lobe and the tip of the right showed extensive cirrhosis in progress. The capsule was much thickened and beneath it were dense collections of lymphocytes extending among the columns of the liver. Bands of fibrous tissue extended to the nearest portal spaces and from these further fibrous septums marked off well defined nodules of liver tissue. Wherever the fibrous tissue was present, lymphocytes were prominent, this being especially notable in the region of the portal spaces. Here, too, there were numerous tortuous bile ducts and endothelium lined spaces which were probably hepatic veins. Small groups of liver cells had been buried in the depths of the connective tissue, and had regenerated to form around adenomatous nodules. The liver tissue itself was infiltrated with lymphocytes, while destruction of the liver cells, atrophy and congestion were prominent features. As has been noted, the liver tissue was for the most part marked into large nodules consisting of many hepatic lobules. The normal radiate arrangement was considerably altered and hepatic central veins were uncommon. Around the edges of the nodules, large, finely granular, deep-staining cells with large nuclei indicated active new cell formation. At other points degeneration was proceeding. This is the hyperplastic adenomatous type of portal cirrhosis. The malignant areas showed dense masses of polygonal, triangular and large oval cells arranged in trabeculae and columns. These cells could be easily recognized by their great irregularity, deep-staining properties and diverse nuclear forms. Mitotic figures were common and multinucleated cells were often seen. Considerable fibrous tissue had developed between the cell columns and a capillary stroma was prominent. In the centers of the nodules degenerative changes were visible, while at the periphery the structure was better preserved. Although most of the nodules had a dense fibrous tissue capsule in which many atrophic liver cells and bile ducts were present, there had been direct invasion of the hepatic substance. It is in these situations that transitional forms are searched for, but it always seems possible to distinguish quite well between normal and malignant cells, that is, the process is an infiltrative one. Many branches of the portal veins were plugged with thrombi of the tumorous cells.

From the cell type and its arrangement there was no doubt that the tumor was a hepatoma or primary carcinoma of the liver cells. In the metastatic nodule from the right auricle, pulmonary artery and lungs, the same type of cell with the same arrangement was seen. In the lungs the tumors were situated within the pulmonary artery and its smaller branches, dilating the lumen and producing marked thinning of the walls.

CASE 3—A man, aged 54, was admitted to the clinic, March 20, 1924, complaining of stomach trouble. Eighteen months previously, after a severe headache, he had vomited a small amount of blood, and a few days later had noticed a hard lump in the left upper quadrant of the abdomen. A second hemorrhage occurred one month later, more severe than the first, leaving him markedly jaundiced, but the jaundice gradually subsided. Fats and coarse vegetables induced epigastric distress with bloating and belching. His weight was well maintained, but he had gradually lost strength.

On examination the patient was found to be well nourished, slightly anemic, with edema of the feet and moderate distention of the abdomen. The liver and spleen were tender and enlarged (Grade 2). The hemoglobin was 44 per cent, erythrocytes numbered 37,300, leukocytes 6,600, and the blood platelets 124,000. The fragility test indicated an increase in red cell resistance. The coagulation time was five minutes, and the prothrombin time ten minutes. A diagnosis of Banti's disease was made. On exploratory operation the condition in the liver was observed and the abdomen closed without further procedure. The patient gradually became weaker, and died twelve hours later.

Necropsy was performed nine hours after death. Primary massive carcinoma of the liver involving the right lobe, ascites, esophageal varices, left hydronephrosis (Grade 4), old healed mitral and aortic endocarditis with hypertrophy of the heart (490 Gm), and fatty and fibrous changes of the myocardium were found.

The abdomen was moderately distended. The peritoneal cavity contained about 1,500 cc of fluid with no evidence of peritonitis. The gallbladder contained 25 cc of thick mucoid bile, the mucosa was normal. The extrahepatic bile ducts, pancreas, stomach and duodenum appeared normal. There were a few varices of the esophagus and a small amount of free blood in the ileum. The liver weighed 2,810 Gm and the right lobe extended 6 cm below the costal margin in the right clavicular line, forming a massive tumor with a coarsely nodular surface. The left lobe was finely granular and had a thickened opaque capsule. Situated on the inferior and the posterior surface of the right lobe was a spherical mass which was slightly elastic to pressure and measured 15 by 13 cm. On section the entire right lobe except a small margin near the hilum was replaced by a greenish white tumor, putty-like in consistency, and surrounded by a firm white capsule from 2 to 3 mm in thickness. Delicate fibrous trabeculae from the capsule divided the tumor into small, irregular masses, and in the meshes of this network lay the pastylike tumorous tissue. In the superior portion was a cavity measuring 3 by 3.5 cm, containing clotted blood, with a similar but smaller cavity just below and to the right. In the adjacent liver tissue near the left lobe were many smaller encapsulated nodules similar in structure to the main mass and apparently metastasizing from it. Grossly it was impossible to determine whether any branches of the portal or hepatic veins were occluded by the tumorous tissue. In the left lobe were bands of connective tissue enclosing small white nodules, giving it the typical cirrhotic character. It was practically free from nodules of the appearance and consistency of those in the right lobe.

Microscopic sections from various parts of the right lobe showed a cirrhotic process generally distributed throughout its whole extent, but more marked in the region of the tumor. The bands of connective tissue surrounded large areas of parenchyma of the liver. The capsule was thickened and from it dense bands of fibrous tissue extended into the hepatic substance marking off circular

areas consisting of numerous individual lobules. The connective tissue contained many tortuous bile canaliculi, most marked at the periphery of these conglomerate masses. Not only was this area infiltrated with large numbers of lymphocytes, but the whole structure of the liver was invaded more or less diffusely and where they were assembled in groups, strands of connective tissue extended irregularly among the hepatic columns. The nodules of liver cells contained a few central sinusoids, most of them being irregularly disposed with regard to the connective tissue, and indeed many appeared incorporated with it. Congestion of the sinusoids was particularly prominent and fatty degeneration was common. The cells at the periphery of the adenomatous masses showed a faintly granular cytoplasm, staining more evenly and deeply than the central cells, the nuclei were clear cut, occasionally double, and with one or two mitotic figures. Bile staining was prominent throughout the section. The tumors consisted of dense masses of more or less polygonal cells having a definite trabecular arrangement well preserved throughout. They stained irregularly and the cytoplasm was vacuolated and coarsely granular. The nuclei varied greatly in size, were pyknotic and hyperchromatic, taking the hematoxylin stain more intensely than the nuclei of the normal liver cell. In many situations the cells had a rosette formation, but no lumen was visible. Multinucleated giant cells and mitotic figures were numerous. Fibrous tissue was not a marked feature among the trabeculae but as the periphery was reached the van Gieson stain revealed it to be well developed. A capillary stroma, however, was prominent throughout. Around each mass were extremely dense bands of homogeneous connective tissue containing a few lymphocytes and vessels filled with columns of tumorous cells. Even after careful search no transitional stages between liver and malignant cells could be demonstrated nor was any intracellular bile pigment found. The nodes at the hilum showed no metastatic deposits. This tumor was a primary liver cell carcinoma or hepatoma of the massive form.

CASE 4—A man, aged 48, was admitted to the clinic, May 28, 1925, complaining of pain in the upper abdomen, nausea, vomiting and belching, with loss of weight and strength. Two years prior to admission, he began to have epigastric pain, which persisted and gradually increased up to the present time, associated with bloating and belching after meals. Twenty-two months after the onset he had daily attacks of nausea and vomiting which continued for three or four weeks, nausea alone remaining after the vomiting subsided. He was forced to stop work. He had lost 20 pounds (9 Kg.) in the last two months.

The patient was slightly emaciated, with dark skin and yellowish conjunctivae. The abdomen was slightly distended and tympanitic. A palpable and tender mass, extending 75 cm. below the right costal margin and over on to the left side, was found in the upper part of the abdomen. It was smooth on the right side but markedly nodular on the left. The whole tumor moved with respiration. A diagnosis of malignant disease of the liver was made, and the patient was admitted to the hospital for observation, where he gradually became weaker and died ten days later.

Necropsy was performed two and one-half hours after death. Primary carcinoma of the liver with invasion of the sixth thoracic vertebra and compression myelitis, gangrenous cystitis (cord bladder) and pyelonephritis, pneumoconiosis 3, old healed pulmonary tuberculosis with tuberculous pleuritis and arteriosclerosis 1 were found.

The skin was universally dark brown and the conjunctivae icteric. There was about 200 cc. of clear yellow fluid in the peritoneal cavity. The spleen weighed 255 Gm. and presented a moderate perisplenitis. Both kidneys showed extensive pyelonephritis, and there was a gangrenous cystitis of the urinary bladder, the mucous membrane being 1 cm. thick, dark brown and necrotic. The pancreas and gastro-intestinal tract were normal. The gallbladder was moderately distended with 80 cc. of black mucoid bile, but there were no lesions.

of the mucosa. The common, cystic and hepatic ducts appeared normal. The liver was enlarged, extending 7.5 cm below the right costal margin. It weighed 3,100 gm. The surfaces of the left lobe and approximately the left half of the right lobe were coarsely nodular and slightly greenish yellow. The remaining surface of the right lobe was studded with minute greenish brown nodules shining through the capsule, which was finely granular throughout. On section the whole of the left lobe was found to be replaced by multiple nodular tumors varying in diameter from 1 mm to 0.5 cm. Each was surrounded by dense bands of grayish fibrous tissue. The branches of the portal vein were occluded by masses of soft velvety green material interspersed with small blood clots. Toward the middle portion of the liver the nodules became more discrete, but even here the portal vessels were seen to be plugged with the same tissue. The portal vein at the hilum was occluded by a red and white striated thrombus in which small masses of yellow material could be recognized. In the right lobe there were many discrete nodules of similar appearance pushing aside and compressing the hepatic tissue. Here the liver was coarsely granular with small greenish areas of tissue surrounded by bands of fibrous tissue. It had the typical appearance of a well advanced cirrhosis.

Microscopic sections were taken from various portions of the liver and from the metastatic tumors. In the areas where tumorous tissue was not grossly evident, an extremely active cirrhotic process was in progress. The periportal spaces were surrounded by dense masses of connective tissue, with fibrous septums extending into the parenchyma. These marked off large areas of hepatic tissue forming circular nodules. The abundance of lymphocytes was striking. They were in great masses between the connective tissue and the liver cells and extended out among the acini of the parenchyma, the sinusoids contained great numbers. Wherever these lymphocytes were collected, destruction of liver cells was in active progress, and a replacement fibrosis was occurring. At the same time hyperplastic and regenerative changes were taking place in the liver cells in these areas, and columns of clear cut, convex and more deeply stained cells crowded into every corner and crevice of the connective tissue. The adenomatous nature of the change was evidenced also by the shape of the nodules which consisted of many individual hepatic lobules with few central veins. The radiate arrangement of the acini had disappeared, and the newly formed nodules bore no relation to the original hepatic structure. Tortuous bile canaliculi were actively growing wherever fibrosis had occurred, although no liver cell regeneration from them could be made out. The area of malignant cells consisted of dense masses of cuboidal cells, having a more or less tubular arrangement, and set in extremely compact fibrous tissue. The cells themselves varied from cuboidal to columnar and formed columns and tubules with small lumina, frequently plugged with bile thrombi. Bile was not visible within the cells but there was no doubt that it frequently occurred in the tubular spaces. The cells themselves stained more deeply than the liver cells and the nuclei were round, oval or distorted, and were composed of granular protoplasm. Mitotic figures were not frequent although there was a tendency to pyknosis. In their staining reactions and general shape they strongly resembled the cells of the bile canaliculi. There was a poorly developed capillary stroma through the tumor, but a large amount of connective tissue. This fibrous tissue was homogeneous, and although it contained few lymphocytes, bile canaliculi were common. In one situation the malignant tubules diffusely invaded the fibrous tissue and infiltrated the hepatic sinusoids. Mixed with them were large numbers of obviously tortuous bile ducts which seemed too numerous and too hyperplastic to be regarded as entirely normal. We are inclined to think, however, that these are not transitional forms. Some of the spaces in which the tumor lay were lined by endothelium, and where retraction from the wall had taken place the endothelium followed the tumor. It seemed, therefore, that these spaces were originally of vascular origin. From the cell

type and its relation to the bile canaliculi this tumor should be classified as a cholangioma or primary carcinoma of the small bile ducts occurring in a cirrhotic liver

CASE 5—A man, aged 60, was admitted to the clinic, Aug 8, 1925, complaining of a sharp pain of three months' duration in the right upper quadrant. The pain was troublesome during the day but not at night, and bore no relation to food. There was neither nausea nor vomiting. Of late his bowels had moved from four to six times a day, and occasionally he had passed a little blood. He had lost about 10 pounds (4.5 Kg) in weight.

On examination the abdomen was tense and tender, particularly from the umbilicus to the navel. A mass was found in the right upper quadrant. There were also signs of fluid in the flanks. A test of hepatic function showed dye retention 3, serum bilirubin was 1.6 mg for each hundred cubic centimeters of blood. The hemoglobin was 57 per cent. An exploratory operation was performed, and extensive cirrhosis of the liver with ascites was found. The liver was about twice the normal size, and on account of the markedly nodular condition malignancy was suspected. The abdomen was closed without further procedure. The patient gradually became weaker and died on the third day.

Necropsy was performed two hours after death. The findings were cirrhosis of the liver with adenoma formation and malignant change, varices of the veins of Sappey and of Ritzius, and of the esophagus, with hemorrhage from the first, plugging of the branches of the portal vein by tumorous tissue, splenomegaly, partial collapse of the lower lobes of both lungs, jaundice 1, multiple retention cysts of both kidneys, old healed tuberculous pleuritis and lymphadenitis, healing gastric ulcer at the pylorus, melanosis of the sigmoid and pseudomelanosis of the cecum, emaciation 3, and arteriosclerosis 1.

The skin was slightly jaundiced. The peritoneal cavity contained about 1,500 cc of fluid, but there were no signs of peritonitis. Between the liver and the diaphragm, especially over the right lobe, were numerous dense adhesions which were broken down with difficulty. The spleen weighed 405 Gm and presented a smooth, slaty blue capsule with slight fibrohyaline changes. On section it was dark red with well marked fibrous change in the trabeculae. The gallbladder contained 15 cc of thick bile and presented a few papillomas of the mucosa. The common and hepatic ducts were patent. The liver weighed 2,645 Gm. The surface was extremely nodular, the nodules varied in diameter from a few millimeters to 10 cm. The largest projected from the right lobe and was densely adherent to the peritoneum covering the diaphragm. These masses were brownish yellow but the intervening tissue, which consisted of finer granulations, were bluish gray, as seen in cirrhosis. The masses were soft, semifluctuant, and in one situation where the capsule had ruptured a yellowish pasty mass was expressed. On section the liver appeared variegated, owing to the presence of multiple globular tumors scattered throughout the substance. The largest, measuring 11 cm in diameter, projected from the right lobe and occupied almost its whole extent. In general, they were fairly sharply defined from the hepatic tissue, which was atrophied and compressed to form a definite capsule for each nodule. The color varied from yellow to light reddish pink, although in many places green predominated, especially in the larger masses. Fibrous trabeculae extended through the substance of the nodules, forming a network, in the meshes of which was embedded soft tumorous tissue of pasty consistency. Degenerative changes and hemorrhages were common in the larger nodules, the smaller ones were firmer and of a more uniform yellow. The intervening tissue had a somewhat distinctive appearance. Here and there were small velvety brownish nodules, much firmer and more circumscribed, and surrounded by definite bands of connective tissue, giving the whole a surface like leather to the touch, and offering considerable resistance to the knife. The portal vein at the hilum was completely occluded by a thrombus of fairly recent date, but the medium sized veins were filled with soft yellow material resembling that seen in the nodules. This condition seemed

to extend out into the smallest recognizable branches of the portal system. There was no extrahepatic metastasis.

Microscopic representative sections were taken from areas throughout the liver. Those from the finely granular portion showed large nodules of apparently normal liver cells surrounded by bands of dense connective tissue. The capsule was thickened and from it extended the fibrous arches which surrounded the hyperplastic nodules. Lymphocytes were extremely numerous beneath the capsule and along these septums. In the periportal spaces, there was a great deal of scarring, the thickening being most marked in the region of the portal vessels. Collections of lymphocytes and many tortuous bile ducts were seen. Small nodules of hepatic tissue had become separated from the parent mass and remained stranded in the depths of the scars. There were no single liver cells or fragments of acini in these septums such as are seen in the intercellular type of cirrhosis, for all nodules showed definite hyperplastic processes, and single cells and portions of acini had become adenomatous masses. The remaining hepatic tissue consisted of large nodules made up of many small lobules with eccentrically placed and frequently absent central veins, where the fibrous bands had extended into the lobule and incorporated the veins in the scarring process. The radiate arrangement of the acini was profoundly altered, especially at the periphery where the cells were larger, more convex, and had the appearance of being newly formed. Fatty degeneration was not a marked feature, although there was considerable congestion of the sinusoids which also contained a good many lymphocytes. Near the malignant masses and incorporated in their capsular walls, were elongated groups of liver cells surrounded by dense fibrous tissue. They were compressed, atrophic and infiltrated with lymphocytes. Here actual necrosis of the cells had taken place and some hyalinization seemed to be occurring. Bile canaliculi containing many bile thrombi appeared in this situation. Within the tumorous capsule the cells lay in masses, chiefly arranged in columns and trabeculae. There was a small amount of capillary stroma between these budlike processes, but it was not a marked feature. Trabeculation of the tumorous cells was more common at the periphery, but toward the center a good deal of dissociation had taken place owing to necrosis. Here the individual units could be recognized as polygonal, triangular and oval cells. They varied greatly in size, the larger being multinucleated and the smaller showing a single, small, fairly deeply staining nucleus. Mitotic figures were common and all the various stages of karyokinesis could be easily followed. In the nodules in which necrosis was not a marked feature, a rosette formation was recognized with a tiny central space in this arrangement. The vessels were plugged with tumorous tissue, and in many situations an expansion of the walls occurred, causing compression and atrophy of the surrounding liver cells. A small amount of bile pigment occurred in the malignant cells themselves, although it was more frequently seen in the connective tissue at the periphery. Despite careful search, transitional forms between the liver and the cancer cells were not recognized. From the cell type and its arrangement the tumor was a hepatoma or primary carcinoma of the liver cells.

The foregoing five cases were observed in 5,976 cases of necropsy, about 0.08 per cent. During the same period, 220 cases of secondary carcinoma of the liver and 127 cases of portal cirrhosis were observed. Thus, primary carcinoma of the liver occurred once in every forty-four cases in which there was metastatic growth, and was associated with 3.9 per cent of cases of cirrhosis.

The sex incidence in cases of primary carcinoma of the liver runs parallel to that in cases of cirrhosis, that is, males predominate. In

TABLE 1—Findings in Five Cases of Primary Carcinoma (Modified from Eggel and as Used by Karsner)

Case	Age, Sex*	Type of Carcinoma	Origin	Carcinoma Type	Changes in Liver			Extrahepatic Metastasis	Duration	Jaundice	Ascites	Edema	Spleen	Liver
					Cells	Bile Ducts	Vessels							
1	44 ♂	Trabecular hepatoma of diffuse form	Liver cells, right lobe	Marked, portal	Liver cell type, frequent mitosis, little necrosis	Proliferative, inter-venous	Marked tumor thrombosis	None	19 days	Slight	Marked	None	Enlarged and palpable	Enlarged and palpable
2	63 ♂	Trabecular hepatoma of massive form	Liver cells, median portion	Moderate, portal	Liver cell type, frequent mitosis	Proliferative, inter-venous	Marked tumor thrombosis	Inferior vena cava and right auricle, pulmonary artery and lungs	3 years 4 months	Moderate	Marked, 3,000 cc	Slight	Normal	Enlarged and palpable
3	54 ♂	Trabecular hepatoma of massive form	Liver cells, right lobe	Moderate, portal	Liver cell type, frequent mitosis	Markedly proliferative, inter-venous	Slight tumor thrombosis	None	18 months	Slight	Marked, 2,500 cc	Marked	Enlarged and palpable	Enlarged (2,810 Gm.), palpable
4	48 ♂	Adenocarcinoma of alveolar type, glandular of diffuse type	Bile duct, left lobe	Marked, portal	Low columnar cuboidal like bile ducts	Proliferative inter-venous	Marked tumor thrombosis	Spine with compression myelitis	2 years 2 months	Moderate	Slight, 200 cc	None	225 Gm	Enlarged (3,110 Gm.), palpable
5	60 ♂	Trabecular hepatoma of nodular type	Liver cells, right lobe	Moderate, portal	Liver cell type, frequent mitosis, necrosis marked	Proliferative, inter-venous	Marked tumor thrombosis	None	3 months	Slight	Slight, 150 cc	Slight	405 Gm	Enlarged (2,645 Gm.), palpable

* In this table ♂ indicates male

TABLE 2—Incidence as Determined by Previous Authors

Author	Cases	Necropsies	Necropsy, per Cent	Cirrhosis, per Cent	
				Hepatoma	Cholangioma
Eggel	164	?	?	86.4	62.5
Goldzieher and von Bokary	18	6,000	0.3	100	42.8
Yamagiwa	42	?	?	74.75	46.7
Karsner ¹⁵	9	?	?	100	100
Winternitz	3	3,700	0.08	100	100
Hale-White ¹⁶	25	18,500	0.13	?	?
Friedl ¹⁷	4	1,200	0.33	100	100
Clawson and Cabot ¹⁸	1	5,100	0.05	100	
Von Glahn and Lamb ¹⁹	6	1,800	0.33	100	100
Mayo Clinic	5	5,976	0.08	100	100

Thus, sixty-two cases occurred in 42,276 necropsies, or 0.14 per cent. The incidence of cirrhosis will be discussed later.

In our five cases the patients were males, while in nineteen cases reported since 1922 by Torland,²⁰ Clawson and Cabot, Helvestine,²¹ Williamson,²² von Glahn and Lamb, Friedl, Friedenwald and Friedl,²³ Lichty and Richey²⁴ and Jaffe,²⁵ all but four were males. In thirty-two cases reported by von Heukelom,²⁶ thirty-one were males. In Yamagiwa's series the female sex is fairly well represented. The condition usually occurs after the fortieth year, although many cases have been reported as occurring in children. Philipp²⁷ reported twelve genuine cases of this kind, and Dansie,²⁸ twenty-five patients under 2½ years. Griffith²⁹

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23 Friedenwald, J., and Friedl, H. Primary Cancer of the Liver, *Am J M Sc* **168** 875-882 (Dec.) 1924.

24 Lichty, J. A., and Richey, D. G. On Primary Carcinoma of the Liver. Report of Three Instances, *Ann Clin Med* **1** 165-169, 1922.

25 Jaffe, R. H. Sarcoma and Carcinoma of the Liver Following Cirrhosis, *Arch Int Med* **33** 330-342 (March) 1924.

26 Von Heukelom, S. Das Adeno-Carcinom der Leber mit Cirrhose, *Beitr path Anat u z allg Path* **16** 341-387, 1894.

27 Philipp, P. W. Ueber Krebsbildungen in Kindesalter, *Ztschr f Krebsforsch* **5** 326-416, 1907.

28 Dansie, C. B. Primary Malignant Growth of the Liver in Infants, with Report of a Recent Case, *Lancet* **2** 228-229 (July 29) 1922.

29 Griffith, J. P. C. Primary Carcinoma of the Liver in Infancy and Childhood, *Am J M Sc* **155** 79-85 (Jan.) 1918.

recorded fifty-seven cases occurring in children under 16 years of age. The ages in our series were between 44 and 63, while the average age in our compiled series was $61\frac{1}{2}$ years, none occurring in patients under 44. From the point of view of age incidence, the cases are divided into those occurring in infancy and those occurring in adult life, past the age of 40.³⁰ It is noteworthy that the congenital cases are rarely combined with cirrhosis and are to be regarded as instances of congenital maladjustment of groups of liver cells.³¹

The clinical diagnosis in the adult form is usually that of cirrhosis of the liver. The cases fall into two main groups, those in which there is a long indefinite history extending up to three years, with a sudden exacerbation and a termination within four months, and those in which there is a rapid progressive course, lasting from three weeks to four months. In the first group the symptoms are those of cirrhosis. Loss of appetite, loss of weight and strength, digestive disturbances, pallor and enlargement of the abdomen extend over a considerable period of time. Pain in the right side of the upper part of the abdomen is frequently complained of. At some stage a sudden exacerbation of symptoms is noted and the patient rapidly fails. Nausea and vomiting and hematemesis with slight jaundice become more marked, and on examination moderate enlargement of the liver with ascites and edema are found. Although it is said that the liver is enlarged in only 50 per cent of cases, our experience is that 75 per cent would be more accurate. As an important diagnostic point Bile insists on fixity of the liver, so that it moves neither with palpation nor with respiration. In the second group the symptoms follow fairly closely the terminal stage of the previous group. The onset may be insidious, but there is a steady, rapid downward course with loss of weight and strength combined with progressive enlargement and fixity of the liver.

Jaundice was present in 65 per cent of Eggel's cases, it was only slight or moderate in all of our cases. There was marked ascites in three cases, in two there was practically none. Edema is rarely extreme and often absent. The spleen was enlarged in three cases, the enlargement in one being responsible for a diagnosis of Banti's disease. Fever is uncommon but may occur.³² A summary of the clinical findings is shown in Table 1.

While the gross appearance of the liver is fairly typical there are several conditions with which it may be confused. It is of course

30 Rolleston, H. D. *Diseases of the Liver, Gallbladder and Bile Ducts*, Ed 2, London, Macmillan Company, 1914, p. 469.

31 Ewing, James. *Neoplastic Diseases*, Ed 2, Philadelphia, W. B. Saunders Company, 1922, p. 682.

32 Ascoli, V. *Cancro primitivo del fegato a decorso febbrile*, *Sunto di due lezioni*, Policlínico (sez. prat.) **31** 445-450 (April 7) 1924.

absolutely necessary to make a careful search for a primary focus, particularly in the suprarenals, breast, kidneys and gastro-intestinal tract. We mention the suprarenals first because, although true hypernephroma is a rare condition, its secondary manifestation in the liver may be identical with a primary carcinoma. We had one such case in which a huge nodular tumor in the liver with no apparent primary lesion elsewhere was responsible for a diagnosis of primary carcinoma. The absence of cirrhosis and the recognition microscopically of a clear celled structure in the looser parts of the tumor caused us to examine the suprarenals carefully. A small nodule, about 1.5 cm. in diameter, was found, and this proved to be an undoubted hypernephroma. Carcinoma of the kidney, or the condition commonly called hypernephroma, will also cause confusion. Tumor thrombi, necrosis, hemorrhages and various degenerations are common, while variations in color and general appearance, such as are found in cases of primary carcinoma, are deceptive. In general, secondary metastatic nodules occur nearer the surface, they are usually a homogeneous yellowish white when small, and tend to show hemorrhage and necrosis when large. The development of fibrous tissue within the nodules causes umbilication, such as is rarely seen in the primary form. There is rarely any accompanying cirrhosis, although slight local mild fibrosis may occur. In its absence the diagnosis of primary carcinoma should be made with the greatest hesitation. There are two other conditions to be guarded against, nodular hyperplasia and syphilis. Nodular hyperplasia is an uncommon condition in which the liver shows multiple adenomas throughout. While it is practically always associated with portal cirrhosis, cases have occurred in which it was absent. The same controversy has raged over the occurrence of cirrhosis with adenoma as with carcinoma, and the same writers express similar views concerning the two. Sabourin held that nodular hyperplasia was the intermediate stage between cirrhosis and carcinoma and that no distinction could be drawn between them. Muir³³ is in agreement with this. We have studied a case in which there was active hyperplasia in the liver cells, but in which one could say fairly definitely that there was no malignancy. The adenomas were an accentuation of the ordinary regenerating nodules and showed well marked hyperplasia, particularly at the periphery. With the tumor thrombosis which frequently occurs, the whole picture of a generalized cirrhosis with exaggerated "hobnails," some undergoing necrosis and softening, may closely resemble carcinoma. A microscopic examination is usually necessary to make the distinction, but even then it is often difficult. With

33 Muir, R. On Proliferation of the Cells of the Liver, *J. Path. & Bacteriol.* **12** 287-305, 1908.

regard to syphilis little need be said. The adult form of *hepar lobatum* rarely causes trouble, but in children it must always be excluded.

We have divided our cases, according to the classification of Yamagiwa, into hepatoma arising from the liver cells and cholangioma arising from the bile ducts. With the possible exception of the massive form which rarely, if ever, arises from bile ducts, there is little to connect the gross and microscopic appearances, and the nodular and diffuse types may arise from both sources. There were four hepatomas and one cholangioma. Of the former, two were massive (Fig 1), one was nodular (Fig 2), and one diffuse (Fig 3). The cholangioma was also



Fig 1—Massive hepatoma involving entire right lobe, fibrous tissue network in the tumor and little degeneration should be noted. cirrhosis in left lobe.

diffuse. While various criteria have been used to distinguish the two types, the difficulty of an accurate diagnosis has been emphasized by all writers. The presence of a well developed capillary stroma in the hepatoma form and its absence in the others constitute, according to von Heukelom, Wegelin³⁴ and Yamagiwa, the most reliable standard for

³⁴ Wegelin, Karl. Ueber das Adenokarzinom und Adenom der Leber, Virchows Arch f path Anat **179** 95-153, 1905.

differentiation. Bile pigment within the cells in cases of carcinoma of the liver cells has been described by Ribbert.³⁵ The type of cell and its arrangement was considered important by Eggel. All of the hepatomas in the series presented cell types of great variety, from polygonal, polyhedral and triangular to round or oval, with cytoplasm staining rather more deeply and being more granular than is usual in normal liver cells.



Fig. 2—Nodular hepatoma showing nodules of various sizes in right lobe with hemorrhage and degeneration, tumor thrombosis and well marked cirrhosis in left lobe.

The nuclei varied greatly in size, some small and some large, all stained deeply, they often were irregular and pyknotic and exhibited frequent mitosis (Fig. 4). Giant cells often occurred containing from one to

³⁵ Ribbert, Hugo. Das Maligne Adenom der Leber, Deutsche med. Wchnschr. 2: 1607-1609, 1909.

five nuclei. The arrangement in all four was trabecular, although in places an adenomatous formation was suggested. It is to be noted, however, that a lumen was not visible in any situation. Winternitz holds that this adenomatous formation is due to anaplasia from energy of cell growth. Rosettes, such as Goldzieher and von Bokay describe, were quite frequent. Bile pigment was present in a few cells, but not



Fig 3—Extensive diffuse primary hepatoma showing tumor thrombosis and well marked cirrhosis

in metastatic areas, although it occurred in large amounts in the intercellular spaces and in the connective tissue at the periphery. A capillary stroma was certainly more prominent in this type of tumor, and it seemed as though the endothelium grew coincidently with it. In two

cases we noted large masses surrounded by endothelium (Fig 5) Necrosis and dissociation of the cell columns was more common in the hepatoma, especially near the center of the nodules, while the structure was better preserved as the periphery was reached

Concerning the cholangioma there are fairly well marked distinctions which enabled one to clinch the diagnosis The cells were in general cuboidal or cylindrical, with clear or only finely granular protoplasm They were only slightly larger than the cells of bile duct epithelium, but approximated fairly closely their general characteristics The nuclei stained deeply and were hyperchromatic with a pyknotic tendency Mitotic figures were much less common and the cells were better differentiated than in the liver cell type (Fig 6) Their arrangement was

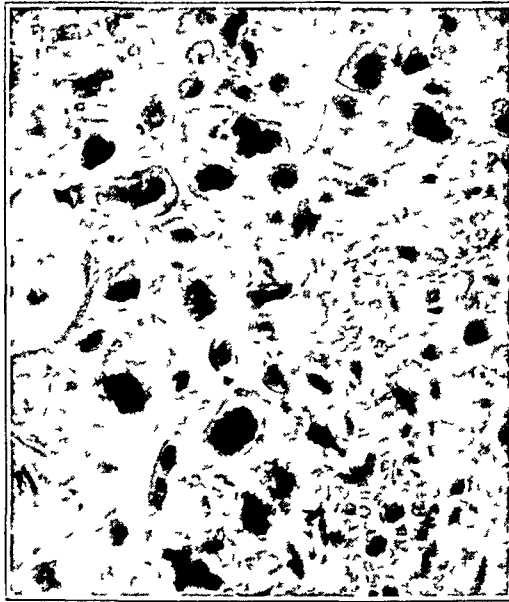


Fig 4—Hepatoma, malignant cells showing variation in size, mitotic figures, giant cells and marked capillary stroma, under higher power

alveolar with definite lumina, often containing bile and biliary detritus With regard to the stroma, capillaries were much less common, but a fine intercellular fibrous network was apparent (Fig 7) In many situations this became concentrated to form dense bands or septums containing little in the way of either normal or malignant cells

We would say that no one feature is sufficient to make a diagnosis of either type Only after a careful examination of the most predominating characteristics can it be decided whether the resemblance is to the liver cell or to the bile duct cell Cell type, stroma, general structure and behavior must all be carefully considered

The question of the multicentric or unicentric origin of these tumors will not be discussed at length In many areas direct invasion and

infiltration of the liver parenchyma by the malignant cells was observed (Fig 8), and here the so-called transitional forms described by von Heukelom, Travis,³⁶ and others were seen. As we were able in every instance to decide which was a malignant cell and which a normal cell, and could find no true transitional forms we must agree with Wintelnitz, Karsner and others that the condition is unicentric in origin and that its spread in the liver is metastatic by way of the portal and the hepatic veins.

The occurrence of extrahepatic metastasis in two of the five cases bears out the figures of others as to its relative infrequency. In one case there was an extension through the hepatic veins into the inferior vena cava, right auricle and pulmonary artery, with small nodules in

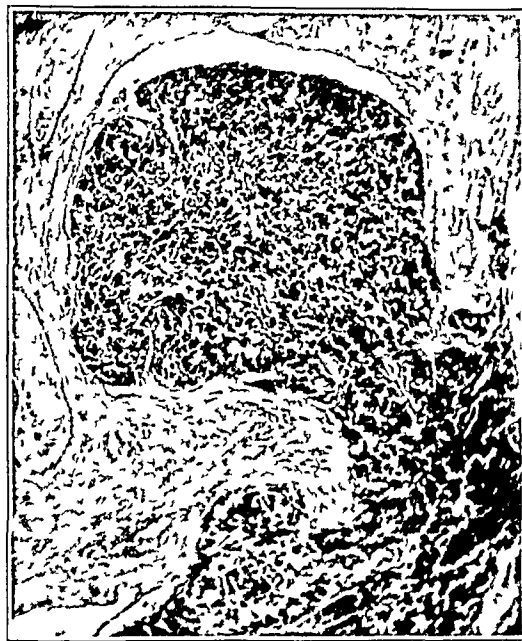


Fig 5—Hepatoma, solitary tumorous nodule in portal vein showing method of invasion, a layer of endothelium covers the tumor where it has retracted from vessel wall.

the lungs. It was similar to a case cited by Wintelnitz. In the second case there was extension to the spine at the level of the sixth dorsal vertebra. The body of this vertebra was replaced by a soft grayish pink mass, which had extended into the vertebral canal on either side of the cord, causing compression myelitis. This form of metastasis is unusual and we can find no parallel to it. In striking contrast to the comparative freedom from extrahepatic metastasis, the extension along the portal and the hepatic veins was remarkable.

36 Travis, Catherine H. A Case of Multiple Primary Adenocarcinoma of the Liver with Cirrhosis, *Bull. Johns Hopkins Hosp.* **13** 108-111, 1902.

Relation to Cirrhosis—Although the earlier statistics of Eggel Goldzieher and von Bokay, and Yamagiwa showed the relation of cirrhosis to vary between 70 and 80 per cent, later work indicated that it is almost a constant feature and that it is the main predisposing factor in the condition. Particularly is this so in the hepatoma form in which, with few exceptions, cirrhosis is present. In the cholangioma form it is not so frequent, but large enough series have not been reported from which to judge. In our case the histories specifically point to cirrhosis in three, while the duration was short in two. It may well be that in those cases in which the onset was sudden the cirrhosis was of the silent type, giving no evidence of its presence until the onset of the malignancy. It is known that cirrhosis may exist for



Fig. 6—Cholangioma, cuboidal and cylindrical cells with tubulo-adenomatous structure buried in dense connective tissue stroma, resemblance to bile ducts and absence of capillary stroma should be noted, tumor thrombosis in left upper corner

long periods and may be discovered only at postmortem examination. In Karsner's twelve cases it was present in all. In Winternitz' cases and in nineteen cases occurring since 1922, all showed cirrhosis. The case of Helvestine is the only one in which it was absent.

The cirrhosis itself has been attributed to many factors: alcohol, syphilis, cardiac disorders¹³ and schistosomiasis³⁷. With regard to the last an interesting fact has been brought to light, in black races, in which cirrhosis due to schistosomiasis is common, primary carcinoma

37 Pirie, J. H. H. Hepatic Carcinoma in Natives of Africa and Its Frequent Association with Schistosomiasis, *M. J. S. Africa* **17** 87-97 (Dec.) 1921

is also relatively common as compared with other forms of malignant disease. Carcinoma in native races is of course extremely rare. Thus, of twenty-one cases of carcinoma which von Hansemann³⁸ was able to record in the examination of 200,000 natives in the German colonies of Africa, four were primary in the liver, a figure out of all proportion to other forms. In the same way Pirie³⁷ found in South African natives thirty-six primary in the liver out of ninety-one of all forms, and of these ten were proved to have had previous cirrhosis due to schistosomiasis.

The points at issue are whether the cirrhosis is primary, secondary or coincident with the carcinoma. It seems that the last view is untenable from the regularity of the appearance of cirrhosis and from its generalized and often severe form. Hanot and Gilbert advanced this



Fig 7—Cholangioma, more solid structure than in Figure 6 with frequent rosettes containing biliary detritus, under higher power, regularity of cells and absence of mitotic figures should be noted

view on the ground that the tumor and the cirrhosis were produced by the same etiologic agent. From an analogy with other cases of carcinoma in which chronic inflammatory processes are almost certainly etiologic, such a view would be hard to maintain, particularly when we examine cases in which cirrhosis has undoubtedly preceded the malignant change. In support of the view of Lancereaux, Wegelin and others, that the presence of a malignant tumor induces cirrhosis, even less can be said. We know that metastatic growths or indeed any

38 Von Hansemann, D. Ueber das Vorkommen von Geschwulsten in den Tropen, *Ztschr f Krebsforsch* 14 39-45, 1914

form of growth will cause localized fibrosis or cirrhotic processes in the liver as in any other organ, but never the generalized and severe form so often seen in this condition. Winternitz has shown, and our cases bear out his statement, that the process is often more severe in proximity to the tumors, but such a thing is easy to understand on the basis that they act as a mild local irritant, just as any foreign body would do. We are in full accord with the view that the cirrhosis is the primary factor and that the malignancy is a change superimposed on it. This has been upheld by von Heukelom, Eggel, Goldzieher and von Bokay, Rolleston³⁰ and many others.

The powers of regeneration possessed by the liver are remarkable. Von Podwyssozki³⁹ first showed that removal of large pieces of liver was quickly followed by regeneration. Mann⁴⁰ has removed four-fifths

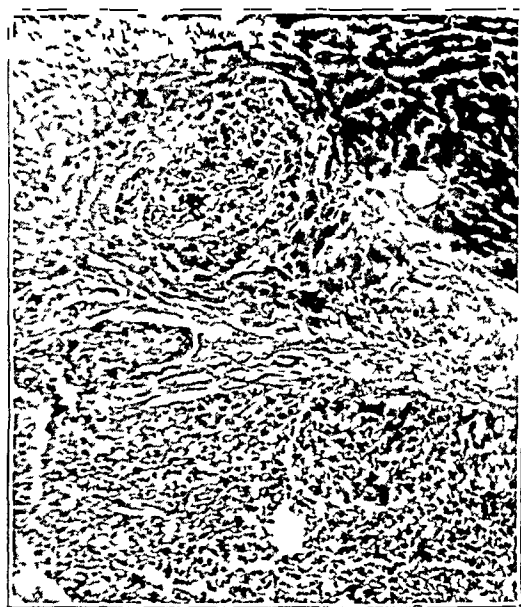


Fig. 8—Hepatoma, tumor thrombus in portal vein, so-called transitional area adjacent to thrombus showing compressed and atrophic liver cells, dense connective tissue and lymphocytic invasion, the tumor cells can be distinguished in the sinusoids.

of a dog's liver with complete regeneration in six weeks. Such regeneration is by cell hyperplasia rather than by cell hypertrophy. In cirrhosis Kretz⁴¹ was the first to point out that the process was one of destruction of the liver cells and that regeneration was a most marked feature. Thus in cirrhosis there is an active destruction and an equally active regeneration with an adenomatous condition of the liver cells.

39 Von Podwyssozki, W. Experimentelle Untersuchungen über die Regeneration der Drüsengewebe, Beitr. z. path. Anat. u. z. allg. Path. **1** 259-360, 1886.

40 Mann, F. C. Studies in the Physiology of the Liver. I, Technique and General Effects of Removal, Am. J. M. Sc. **161** 37-42 (Jan.) 1921.

41 Kretz, R. Cirrhosis of the Liver, Internat. Clin. **3** 289-297, 1905.

most pronounced in the portal type. Buried in the connective tissue are bile canaliculi about which so much controversy has arisen. MacCallum⁴² and others regard them as bile ducts and ascribe to them the power of producing liver cells. The latter is denied by Muir³³ and by Mallory⁴³. Rolleston is of the opinion that they are not bile ducts, but atrophic liver cells. We agree with Muir in this connection that the bile canaliculi are of biliary origin, but that they do not form liver cells. From a close microscopic examination of many cirrhotic livers we have never convinced ourselves that regeneration of liver cells from bile ducts takes place. Whatever the factors may be producing the cirrhosis, it seems that the path of entry is either the portal or biliary channels. Undoubtedly the most common is the portal, and consequently the annular type of cirrhosis is more frequent. In a mild case destruction



Fig. 9—Cirrhosis, showing active destruction of peripheral cells with formation of hyperplastic adenomatous nodules, absence of central veins and radiate arrangement, and extensive lymphocytic invasion in connective tissue stroma adjacent to hepatic cells should be noted

of cells takes place in the neighborhood of the portal spaces with the consequent laying down of new connective tissue. For the continuation of this process two factors are necessary, cell death with the continuous action of a toxin. The rapidity of the process and its extent will be profoundly modified by a third factor, regeneration of the liver cells and bile ducts.

42 MacCallum, W. G. Regenerative Changes in Cirrhosis of the Liver, *J. A. M. A.* **43** 649-654 (Sept. 3) 1904.

43 Mallory, F. B. Cirrhosis of the Liver, Five Different Types of Lesions from Which It May Arise, *Bull. Johns Hopkins Hosp.* **22** 69-75, 1911.

The gross appearance of the liver will vary with the balance maintained by these three factors. We believe that in the portal type the toxic agent affects primarily the cells in the neighborhood of the portal spaces and, second, any group of cells without reference to the so-called hepatic lobule. In the biliary type the toxic agent is more confined to the bases of Sabourin's acini, this results in a more anatomic distribution and so-called monolobular fibrosis. Nevertheless, we would emphasize the fact that in neither type is the classification of cirrhosis based on an anatomic appearance justifiable, for the process is governed by the resultant of the three factors mentioned, and not by the influence of the individual lobule. As biliary cirrhosis is more uncommon and less severe than portal cirrhosis regeneration is not such a marked feature, and hence it is rarely seen in conjunction with carcinoma. In the portal type, for instance, a small section of a lobule, or even large masses of liver cells, are destroyed, often including several hepatic lobules, but, provided a few healthy cells remain, the most extraordinary regeneration will take place.

We have indicated in the microscopic examination of these cases the large nodules of liver tissue devoid of central veins and any radiate arrangement, which could only have been produced by a complete new formation. Evidence of the regeneration is found at the periphery of the nodule. The cells are larger, more convex, with clearer and more acidophilic cytoplasm. The nuclei are larger, often double, and occasional mitotic figures can be detected (Fig 9). MacCallum⁴⁴ has demonstrated this last point clearly. In short, we have primarily an active cell destruction with coincident cell regeneration and formation of hyperplastic adenomatous areas of liver tissue. Within the connective tissue the same hyperplastic change is proceeding, with a tremendous increase in the number of bile canaliculi. The same evidence of hyperplasia can be seen in them. Whether the budlike structures sometimes seen at their ends are liver cells we are not prepared to say. If it were so and we ascribe to both the liver cells and the bile ducts the power of malignant proliferation, then we must admit the possibility of liver cell carcinoma arising from bile ducts. There is no doubt that embryologically liver cells and bile ducts have a common origin, but we believe that in the fully differentiated organism, cells which were originally totipotent become and remain unipotent. In short, to take the case in point, bile ducts produce bile ducts and carcinoma of bile ducts, while liver cells are capable of reproducing themselves to the point of malignancy. The first step in the chain of events is the long continued chronic hepatitis with adenoma formation. Most cases are of this type.

44 MacCallum, W. G. Regenerative Changes in the Liver After Acute Yellow Atrophy, *Rep. Johns Hopkins Hosp.* **10** 375-384, 1902.

If the process is extremely rapid or if the regenerative capacity of the cells is great, nodular hyperplasia occurs. As has been pointed out, many writers make no distinction between this and carcinoma, holding that the three conditions, adenoma, nodular hyperplasia and carcinoma, insensibly shade off into each other. Such an occurrence would be easy to understand were it not for the great rarity of carcinoma compared with the frequency of cirrhosis and regenerative changes in the liver. There can be little doubt that some specific factor or specific change in environment is responsible for the transition from hyperplastic to malignant cells, a condition that removes the barrier confining their biologic function of growth and regeneration within normal limits. Be that as it may, we are of the opinion that from 3 to 4 per cent of cases of cirrhosis will develop into carcinoma as the direct result of the changes induced by the chronic inflammatory condition.

SUMMARY AND CONCLUSIONS

1 Five cases of primary carcinoma of the liver are described: four hepatomas or primary carcinomas of the liver cells and one cholangioma or carcinoma of the bile ducts.

2 The gross and microscopic appearances have little in common, so the massive, nodular and diffuse forms appear in any microscopic type. The massive form is, however, usually derived from liver cells.

3 All the cases were associated with intrahepatic metastasis by way of the portal and the hepatic veins, but in only two were there extra-hepatic growths.

4 No transitional forms were found and the origin is therefore believed to be unicentric.

5 All the cases were associated with cirrhosis of the portal type. The histories in three cases point to a preceding cirrhosis, and in all the microscopic examination of the connective tissue indicated a long standing process.

6 The relation between the hyperplastic liver tissue and the malignant cells is emphasized.

7 From 3 to 4 per cent of cases of cirrhosis, particularly of the portal type, will become carcinomatous.

THE EFFECT OF LIVER DAMAGE ON CHOLECYSTOGRAPHY IN DOGS BY THE USE OF SODIUM TETRA-IODOPHTHALEIN *

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AND

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The visualization of the gallbladder for diagnostic purposes was made possible through the observation of Abel and Rowntree¹ that halogen compounds of phenolphthalein are excreted almost wholly by the liver. Application of this principle to cholecystography was first made by Graham and Cole,² who found that by injecting intravenously tetra-iodophenolphthalein and tetrabromphenolphthalein the gallbladder could be rendered opaque to roentgen rays and therefore visible.

Tetra-iodophenolphthalein was first condemned by Graham and Cole as being too toxic for clinical use, probably they employed an impure product. Observations from this laboratory, however, have shown that with a more purified salt the toxicity of both compounds is the same. But since the opacity to roentgen rays of sodium tetra-iodophenolphthalein is twice as great as that of tetrabromphenolphthalein a good shadow of the gallbladder can be obtained by a dose only one-half as large. This means that the iodine salt is practically only one-half as toxic, and therefore to be preferred for cholecystography.

Theoretically the visualization of the gallbladder by these drugs is based on the power of this organ to concentrate substances excreted by the liver in the bile.

For the purpose of the test a sterile solution in distilled water of sodium tetra-iodophenolphthalein is injected intravenously and roentgenograms of the gallbladder taken from about eight to ten hours following the injection, at which time the concentration of the drug in the gallbladder is supposed to be at its height. A fairly good shadow of the gallbladder is also obtained by the oral administration of the drug in "enteric" coated pills, devised in the clinics of the Peter Bent Brigham Hospital. Details concerning the subject have been published

* From the Laboratory for Surgical Research, Harvard Medical School

1 Abel and Rowntree. *J Pharmacol & Exper Therap* **1** 233, 1909

2 Graham, E. A., and Cole, W. H. Roentgenologic Examination of the Gallbladder, *J A M A* **82** 613 (Feb 23) 1924. Graham, E. A., Cole, W. H., and Copher, G. H. Visualization of the Gallbladder by the Sodium Salt of Tetrabromphenolphthalein, *J A M A* **82** 1777 (May 31) 1924

elsewhere³ Suffice it to say here that one or the other of these methods have been utilized in about 200 cases at the Peter Bent Brigham Hospital with very good results With twenty-eight patients upon whom operations were performed, this method of diagnosis proved to be correct in 93 per cent Other clinics, including that of Dr E A Graham, have made similar reports

The purpose of this study was twofold (1) to determine the effect of sodium tetra-iodophenolphthalein on animals in the presence of an experimentally damaged liver (since as noted in the foregoing the salt is normally excreted almost wholly by the liver), and (2) on the production of cholecystograms by use of this drug under similar conditions

MATERIAL AND METHODS

It has been shown by numerous workers in this country as well as in Europe that when administered to various animals—cats, dogs, rabbits—chloroform acts as a poison leading to degenerative changes of the viscera, particularly the liver The lesions found in the liver are usually defined as central necrosis or fatty degeneration Of special interest in that respect are recent experiments by Davis and Whipple⁴ to the effect that the degree of liver damage depends (1) on the diet on which the animal was kept prior to the experiment, and (2) on the amount of chloroform used during anesthesia In the experience of these workers chloroform given after fasting will produce hepatic damage that is in direct proportion to these two factors "The uniformity of liver injury produced in a dog after three to four days of fasting," say these authors, "is remarkable" In their experiments they used mostly puppies from 5 to 6 pounds (about 2 kg) in weight The animals were starved for from three to four days and then kept under anesthesia for from sixty to seventy-five minutes The amount of chloroform given was not stated in their protocols

In the experiments that follow, the methods of Whipple and Davis for the production of damage of the liver by chloroform were utilized

Dogs were used in all the experiments The animals were isolated and kept on water only for from one to three days At the end of the starving period they were anesthetized with chloroform by the drop method The duration of the anesthesia as well as the amount of chloroform used is indicated in the tables Twenty-four hours after the administration of chloroform, when the liver damage usually reaches

3 Whitaker, L R, and Milliken, G A Comparison of Sodium Tetra-bromphenolphthalein with Sodium Tetra-Iodophenolphthalein in Gallbladder Radiography, *Surg, Gynec & Obst* **40** 17 (Jan) 1925 Milliken, G, and Whitaker, L R The Clinical Use of Sodium Tetra-Iodophenolphthalein in Cholecystography, *Surg, Gynec & Obst* **40** 646 (May) 1925

4 Davis, N C, and Whipple, G H The Influence of Fasting and Various Diets on the Liver Injury Effected by Chloroform Anesthesia, *Arch Int Med* **23** 613 (May) 1919

its maximum, a sterile 10 per cent solution of sodium tetra-iodophenolphthalein in the amount of 0.18 gm per kilogram of body weight⁵ was injected intravenously. Cholecystography was performed from six to eight hours after the injection of tetra-iodophenolphthalein, at which time the concentration of the drug approaches its maximum, and therefore renders the gallbladder opaque. Most of the animals were operated on for the purpose of obtaining a piece of liver for histologic examination, usually about thirty-six hours after the administration of chloroform and from twelve to sixteen hours after the injection of tetra-iodophenolphthalein. Tissues were fixed in formaldehyd, stained with the usual stains, and with Heixheimer's stain for the presence of fat.

TABLE 1—*Summary of First Series of Experiments*

Dog*	Weight, Kg	Fasting Period, Days	Amount of Chloroform Used, Cc	Duration of Narcosis, Minutes	Amount of Drug Used per Kilogram of Animal Weight, Gm	Cholecystography	Pathologic Changes in Liver
1	6.0	3	40	60	0.18	Negative	Extensive central necrosis and fatty degeneration (Fig 1)
2	7.0	3	60	60	0.18	Negative	Extensive central necrosis slight fatty degeneration
3	7.5	3	45	60	0.18	Negative	Same as Dog 2 (Fig 2)
4	7.1	3	25	60	0.18	Negative	About one half of liver lobule necrotic fatty infiltration of remaining cells
5	5.4	3	18	30	0.18	Negative	About one third of liver lobule necrotic, fatty infiltration
6	6.1	3	12	30	0.18	Negative	Same as Dog 5 (Fig 3)

* All dogs used were puppies

EXPERIMENTS

The experiments can be divided into three series according to the weight of the animals, the amount of chloroform used in each instance, the duration of narcosis, and the starving period.

Series 1 includes six young dogs (Dogs 1-6).

From Table 1 it will be seen that (1) animals used in these experiments were from 5.4 to 7.1 kg in weight, (2) the duration of narcosis was from one-half hour (Dogs 5 and 6) to one hour, (3) the amount of chloroform given varied, in Dog 5 being only 18 cc, and in Dog 6 only 12 cc⁶. It is also to be noted (4) that none of the animals of this

5 This is the optimum dose for producing an opaque gallbladder in healthy dogs, in which this amount is well tolerated. Furthermore, it has been found in this laboratory that 0.18 gm of the drug per kilogram of body weight produced no hepatic lesions unless repeated at intervals of a few days over a period of several weeks.

6 In previous experiments of Whipple and Sperry (Whipple, G. H., and Sperry, J. A. Chloroform Poisoning, Liver Necrosis and Repair, Bull. Johns Hopkins Hosp. 20:278 [Sept.] 1909) about 45 cc of chloroform were always used.

series gave a positive shadow of the gallbladder, and (5) that the dogs with a damaged liver usually tolerated the drug well

Figures 1, 2 and 3 show photomicrographs from liver sections taken from Dogs 1, 3 and 6. As seen from the figures, in Dog 1 only a narrow margin of normal appearing liver remained around the portal areas. The rest of the liver lobule was necrotic. In Figure 2 the liver lobule can be divided into three zones: (1) periportal, consisting of normal appearing liver cells which are, however, infiltrated with fat, (2) a narrow band of cells showing complete fatty degeneration, and (3) central necrosis, which occupies more than one-half the lobule.

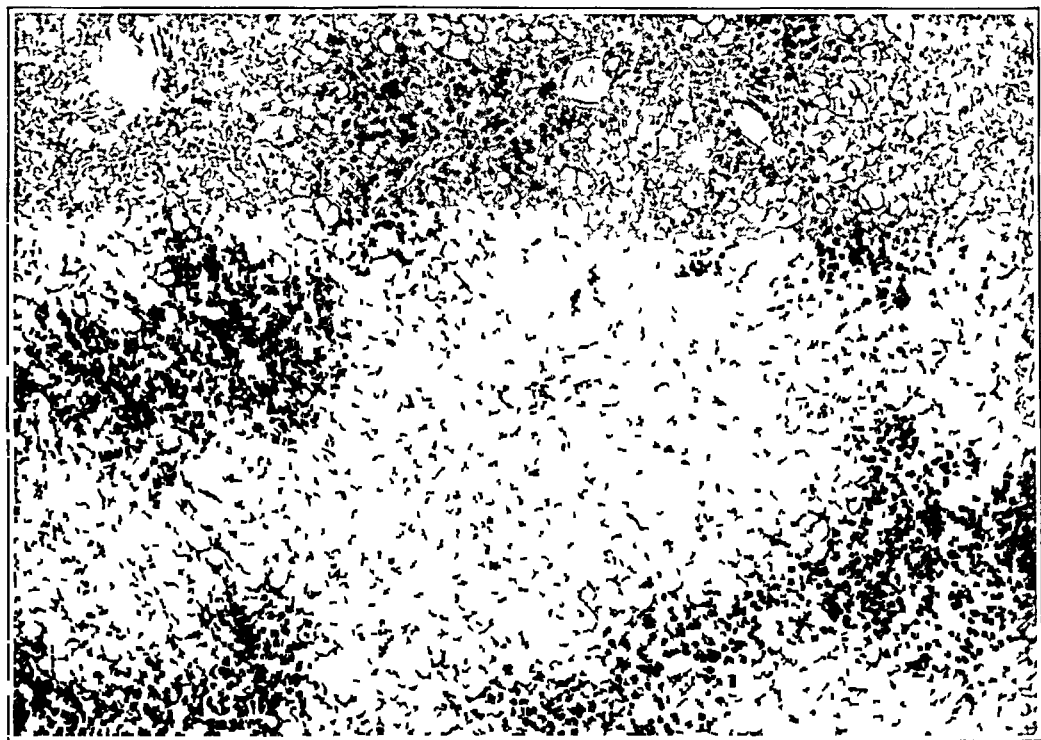


Fig 1 (Dog 1) —Section of liver showing extensive central necrosis and fatty degeneration, hematoxylin-eosin, $\times 80$

In Figure 3 almost one-half the lobule shows fatty infiltration. There are a few necrotic cells around the central vein.

From the first series of experiments we therefore conclude

- 1 Cholecystography with sodium tetra-iodophenolphthalein in dogs in which the liver lobule is extensively damaged by chloroform (fatty degeneration, central necrosis) is negative

- 2 Dogs in which the liver shows a central necrosis occupying more than one-half the lobule as a rule tolerate the drug fairly well⁷

⁷ It is interesting to note here that in complete biliary obstruction the toxicity of the drug, as shown in this laboratory by Maddock and Whitaker, is only slightly increased.

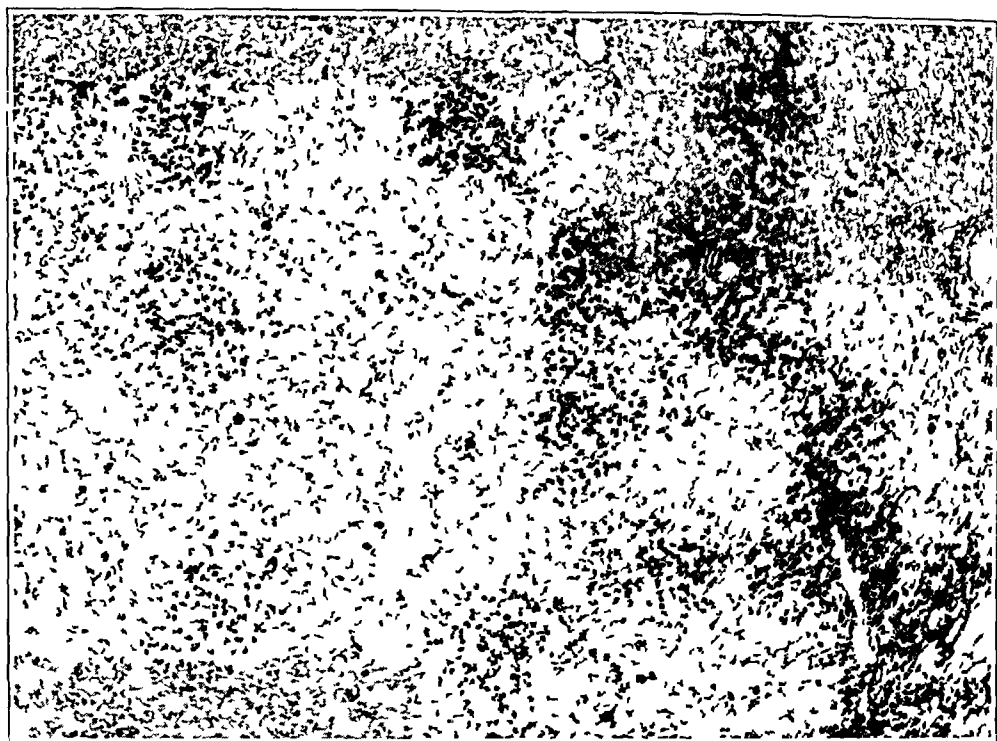


Fig 2 (Dog 3) —Section of liver showing central necrosis of about one-third the liver lobule, hematoxylin-eosin, $\times 80$

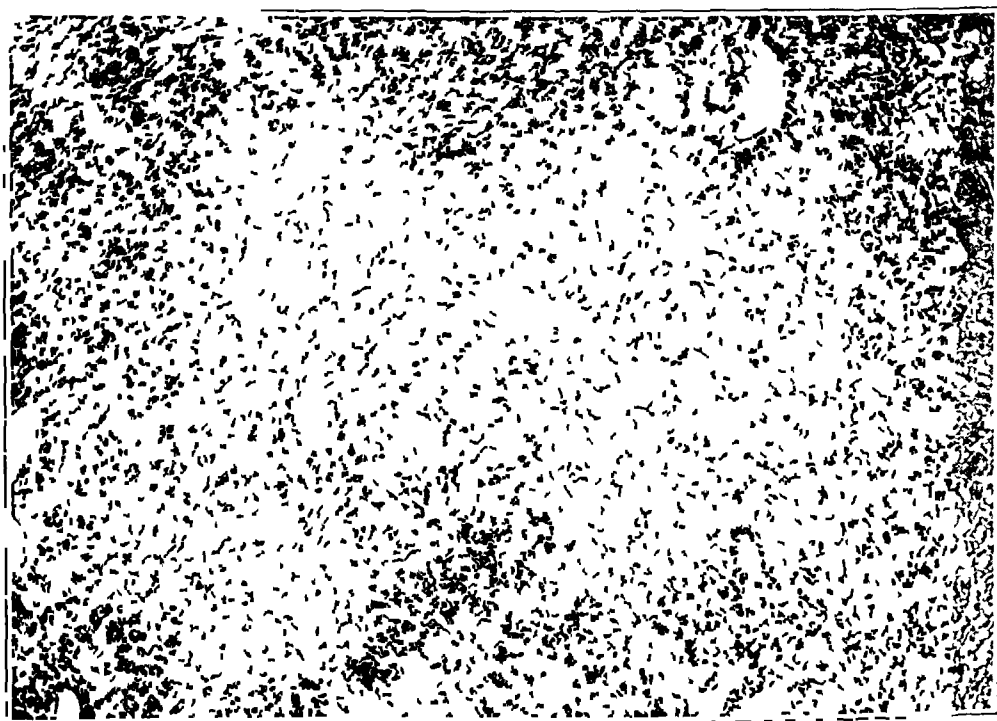


Fig 3 (Dog 6) —Section of liver showing fatty degeneration of more than one-half the liver lobule, hematoxylin-eosin, $\times 80$

3 Starvation for three days followed by the administration of small amounts of chloroform (12 c c in one case) over one-half hour leads to an extensive damage of the liver

SECOND SERIES OF EXPERIMENTS

The second series of experiments differed from the first in that (1) full grown large dogs were used, (2) the fasting period was reduced from three days to twenty-four hours, and (3) the amount of chloroform administered was in some instances reduced to a minimum of 6 c c

The purpose of these experiments was to produce a *minimum* liver damage and thus to ascertain whether such a liver would excrete the drug in an amount sufficient to render the gallbladder visible

TABLE 2—*Summary of Second Series of Experiments*

Dog	Weight, Kg	Fast-ing Period, Days	Amount of Chloroform Used, C c	Dur a-tion of Narcosis, Minutes	Cholecys tography	Pathologic Changes in Liver
7	7.4	1	20	30	Negative	Extensive central necrosis, fatty infiltration of remaining cells (Fig. 4)
8	9.0	1	10	20	Positive	Central necrosis, about one sixth of liver lobule
9	13	1	11	20	Pos itive	A few necrotic cells around the central vein, fatty infiltration, one third of lobule
10	17	1	10	10	Positive	Fatty infiltration, about one fourth of liver lobule
11	14.8	1	10	10	Positive (faint)	Fatty infiltration, no necrosis (Fig. 5)
12	13.8	1	12	10	Positive	Fatty infiltration, about one half of lobule (Fig. 6)
13	17	1	12	12	Positive (faint)	Almost similar to Dog 12 (Fig. 7)
14	12.3	1	6	10	Positive	Fatty infiltration, about one third of liver lobule
15	20	1	6	10	Positive	Almost similar to Dog 14

Of the series of nine dogs only one (Dog 7) gave a negative cholecystogram. Figure 4 shows the large amount of liver damage produced in this animal. It is of interest to note that only 20 c c of chloroform administered during a period of thirty minutes produced an extensive lesion of the liver in an animal that had been fasting for twenty-four hours. Of the other eight animals two gave faint shadows, and six were frankly positive. In two of those with faint shadows the liver, as illustrated in Figure 6, showed considerable damage.

A fatty infiltration of the liver mostly confined to the central area but also conspicuous all over the lobule was likewise observed in Dogs 8, 13, 14 and 15, all of which gave frankly positive cholecystograms, showing that a shadow can be obtained in the presence of fairly extensive damage to the liver.

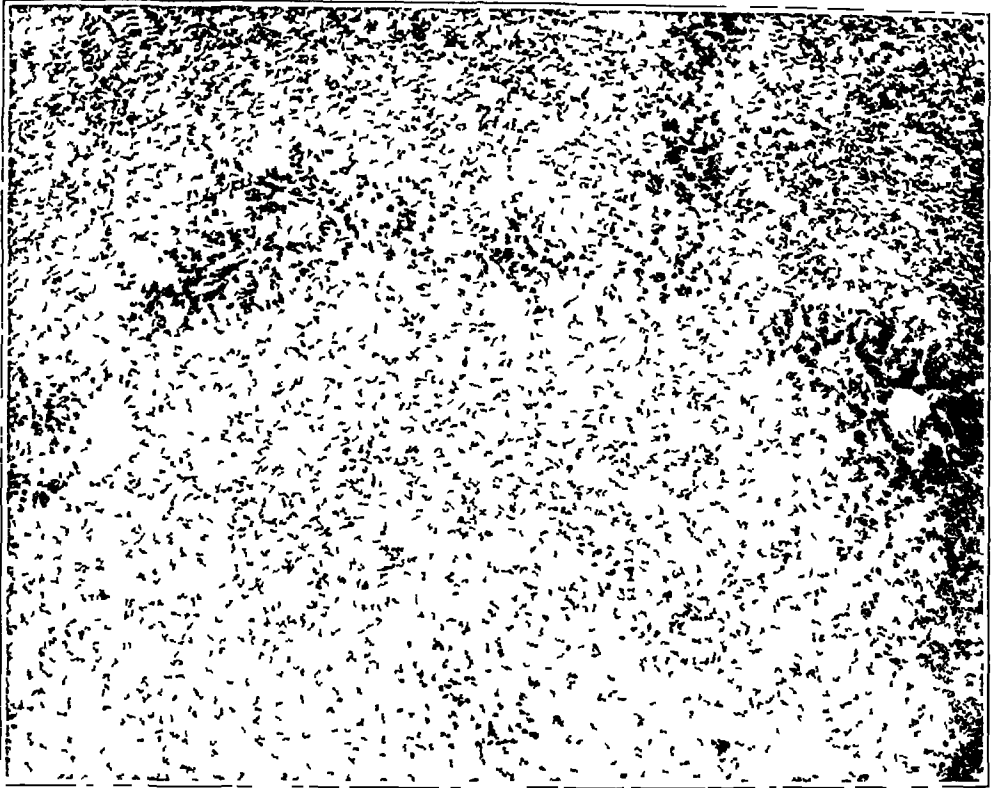


Fig 4 (Dog 7) —Section of liver showing extensive central necrosis and fatty infiltration of remaining cells, hematoxylin-eosin, $\times 80$

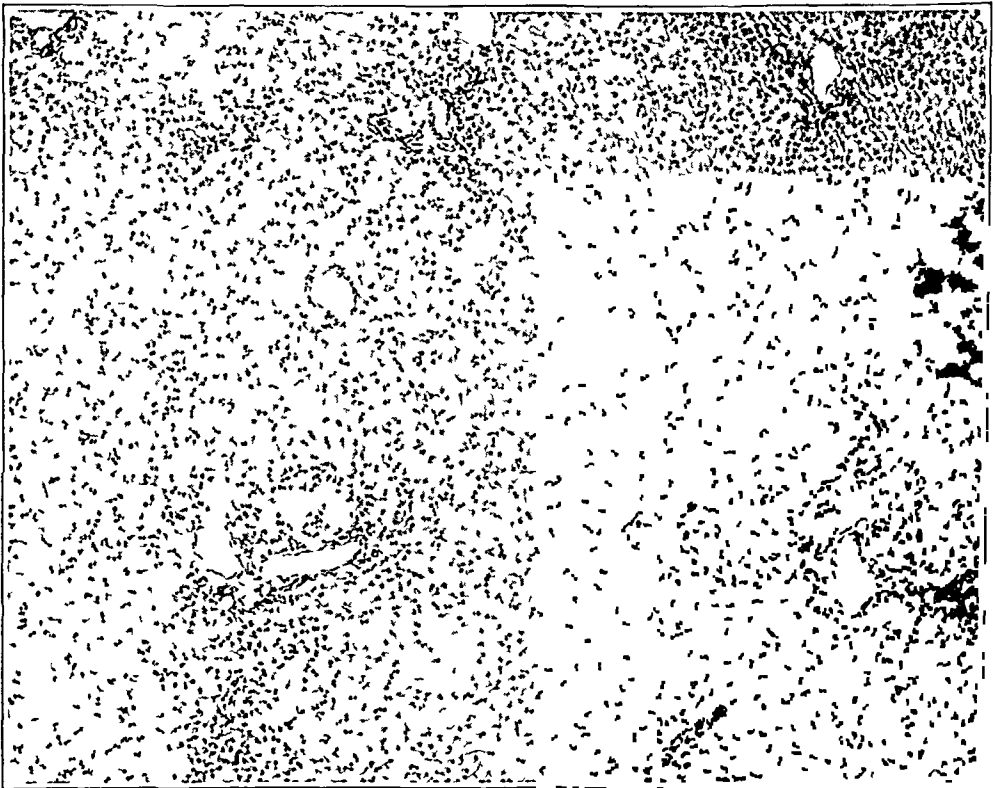


Fig 5 (Dog 11) —Section of liver showing fatty degeneration of more than one-half the liver lobule, hematoxylin-eosin, $\times 80$

Figure 5 (Dog 11) shows the amount and type of injury to the liver produced by only 10 c c of chloroform. Figure 6 illustrates the extent of degeneration compatible with a positive cholecystogram.

These experiments confirm in general those made by Davis and Whipple. It may be added that in starved animals quite extensive necrosis was produced with much smaller doses of chloroform than used by these workers.

From this second series of experiments we conclude, as in the first series, that an extensive lesion of the liver interferes with its excretory

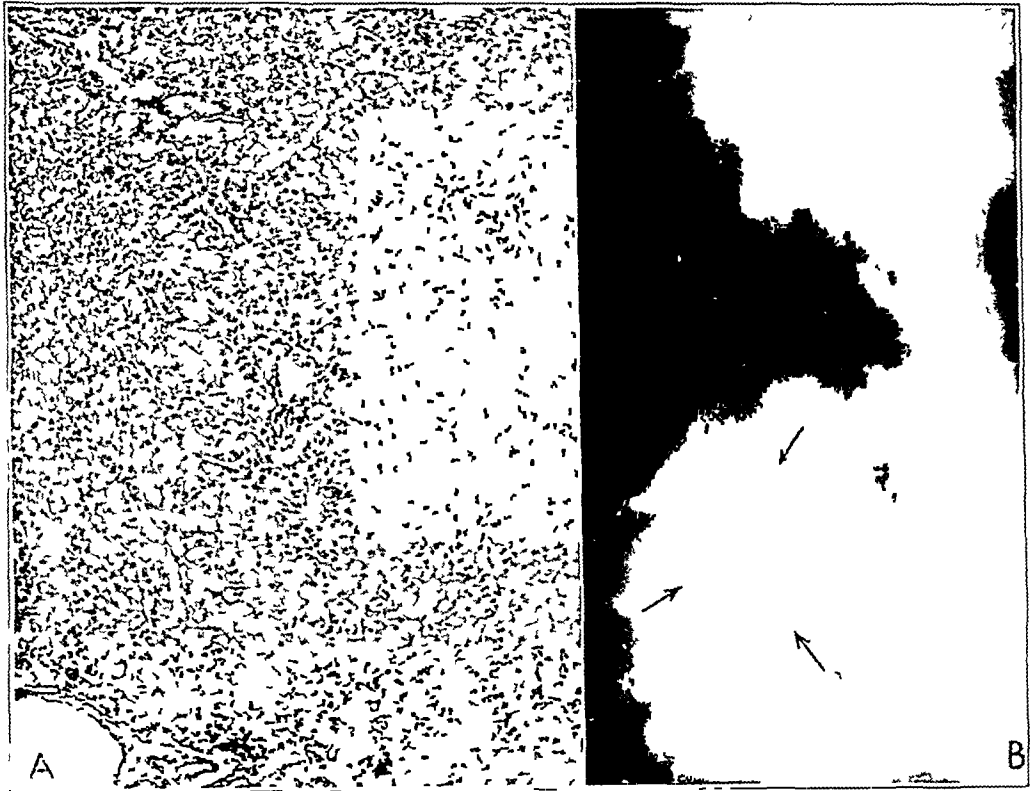


Fig 6 (Dog 12) —*A*, section of liver showing fatty degeneration of about one-half the liver lobule, hematoxylin-eosin, $\times 80$, *B*, cholecystogram showing positive shadow of gallbladder (arrows) in same dog

function, and consequently with cholecystography, but that a moderately damaged liver (slight central necrosis, fatty infiltration) does not interfere with cholecystography in dogs by the use of sodium tetraiodophenolphthalein (Fig 6)

THIRD SERIES

The third series includes six dogs (Dogs 16-21) that were not subjected to starvation, having been anesthetized with chloroform immediately after taking food.

Table 3 shows the amounts of chloroform given and the duration of the narcosis. It will be seen that the amount of chloroform administered

TABLE 3—*Summary of Third Series of Experiments*

Dog	Weight, Kg	Fasting Period	Amount of Chloroform Used, C c	Duration of Narcosis, Minutes	Cholecystography
16	10	None	10	10	Positive
17	15	None	15	10	Positive
18	19	None	15	15	Positive
19	20	None	15	15	Positive
20	19.3	None	18	17	Positive
21	14.2	None	15	15	Positive

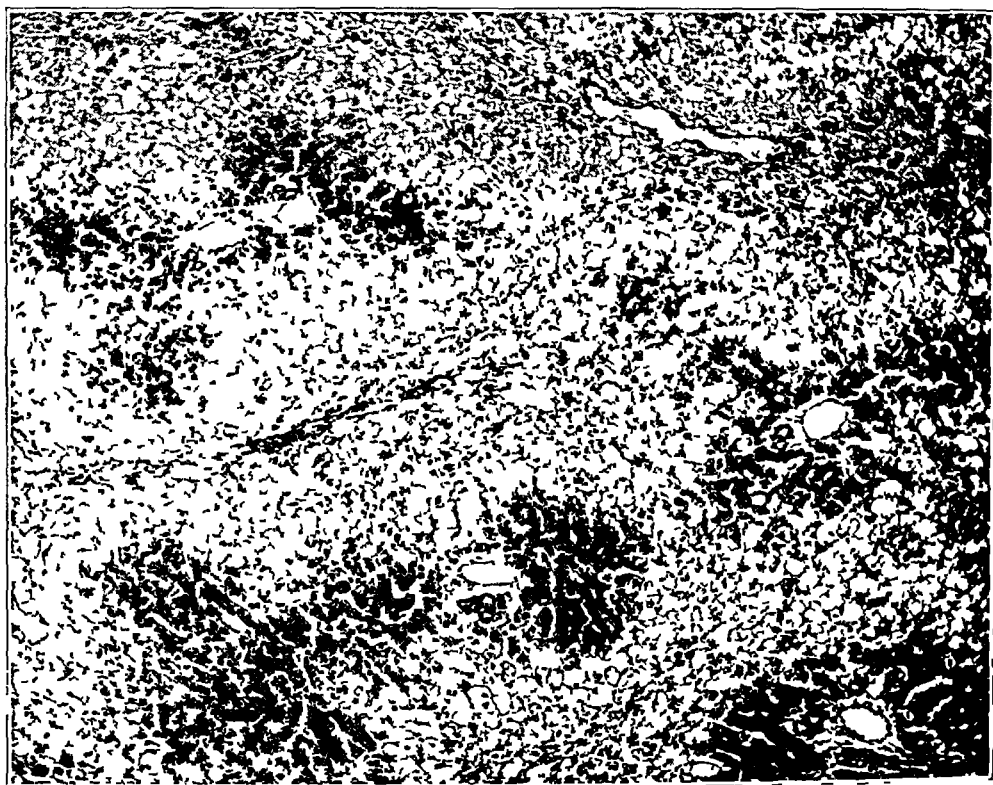


Fig 7 (Dog 13) —Section of liver showing changes almost identical with those in Dog 12 (Fig 6)

to each dog of this series is higher than that used in the second series of experiments, with the exception of Dog 7. The duration of narcosis was from ten to seventeen minutes. On histologic examination the livers of three animals that were killed (Dogs 16, 20 and 21) showed a narrow central zone of fatty infiltration with an occasional polymorphonuclear leukocyte. In all the six animals clear shadows of the gallbladder were obtained. There is, then, an additional interest in this series of experiments, since it shows that starvation is apparently one of the primordial factors in the production of liver damage by the use of chloroform.

CONCLUSIONS

The purpose of the present study has been (1) to determine the toxicity of sodium tetra-iodophenolphthalein in dogs in which the liver was damaged by the use of chloroform as an anesthetic, and (2) the degree of excretion of the drug by a liver thus damaged as determined by cholecystography

The results have shown that a moderately damaged liver does not interdict the use of sodium tetra-iodophenolphthalein, for the animals with a liver so damaged tolerate the drug apparently as well as normal animals

Because of the much smaller amount of sodium tetra-iodophenolphthalein routinely used in patients (one-fourth) than used with safety on dogs known to have more or less extensive hepatic damage, the existence of presumed or obvious hepatic disease in human beings should not necessarily preclude the employment of the drug for purposes of cholecystography in the clinic

CARBON MONOXID POISONING

A COMPARISON OF THE PRESENT METHODS OF TREATMENT*

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In 1920 Henderson and Haggard¹ published the results of experimental treatments of dogs asphyxiated by carbon monoxid. The rate of fall of the carbon monoxid hemoglobin was studied in control dogs and in dogs treated with air containing 6 per cent and 10 per cent carbon dioxid and with oxygen containing 10 per cent carbon dioxid. As a result of these experiments they advocated the use of a mixture of carbon dioxid in oxygen for carbon monoxid poisoning. In later papers² the same workers have recommended the use of a mixture of 95 per cent oxygen and 5 per cent carbon dioxid for resuscitation from carbon monoxid asphyxia, from ether or alcohol intoxication and for respiratory failure due to other causes, such as morphin narcosis. In the discussion following the reading of one of these papers,³ Dr R R Sayers, chief surgeon of the Bureau of Mines, stated that at that stage of his experiments pure oxygen seemed to give better results as to relief of symptoms, and almost as rapid elimination of carbon monoxid from the blood as did the carbon dioxid-oxygen mixture.

Sayers and Yant⁴ as a result of experiments on human subjects now recommend the use of pure oxygen, and also recommend that physicians use the carbon dioxid-oxygen mixture when possible, and note the results. It is to be remarked here that the carbon dioxid-oxygen mixture they used contained approximately 10 per cent of carbon dioxid.

* From the Medical Research Division of Edgewood Arsenal

1 Henderson, Yandell, and Haggard, H W. The Elimination of Carbon Monoxid from the Blood After a Dangerous Degree of Asphyxiation, and a Therapy for Accelerating the Elimination, *J Pharm & Exper Therap* **16** 11-20 (Aug) 1920

2 Henderson, Y, Haggard, H W, and Coburn, R C. The Therapeutic Use of Carbon Dioxid After Anesthesia and Operation, *J A M A* **74** 783-786 (March 20) 1920. Henderson, Y. Resuscitation from Carbon Monoxid Asphyxia, *J A M A* **83** 758-763 (Sept 6) 1924. Haggard, H W, and Henderson, Y. The Treatment of Carbon Monoxid Poisoning, *J A M A* **77** 1065-1067 (Oct 1) 1921

3 Haggard and Henderson (Footnote 2, third reference)

4 Sayers, R R, and Yant, W P. The Elimination of Carbon Monoxid from Blood, by Treatment with Air, with Oxygen, and with a Mixture of Carbon Dioxid and Oxygen, *Pub Health Rep* **38** 2053-2074 (Sept 7) 1923

More recently, Haldane,⁵ while stating that the carbon dioxid-oxygen mixture is the best known remedy for carbon monoxid poisoning points out that the great weight of the gas cylinders required is a disadvantage. In the absence of the carbon dioxid-oxygen cylinders he recommends the use of a carbon dioxid-air mixture, and describes an easily portable apparatus that will give a from 3 to 5 per cent mixture of carbon dioxid in air for five hours. He also states that this treatment gives immediate relief from severe symptoms and probably washes out carbon monoxid from the body more rapidly than if pure oxygen were used. Henderson, Haggard and Coburn⁶ also have described a simple apparatus for administering carbon dioxid-air mixtures.

Nicloux, Nerson, Stahl and Weill⁷ disagree with the findings of Henderson and Haggard so far as the superiority of air plus carbon dioxid, 5 per cent over pure oxygen, is concerned. They found oxygen to be superior to the carbon dioxid-air mixture. They also found that oxygen plus 5 per cent of carbon dioxid acts slightly faster than pure oxygen in washing out carbon monoxid from the blood. It has been seen that Henderson and Haggard worked with a 10 per cent mixture of carbon dioxid in oxygen, while Nicloux and his co-workers used a 5 per cent mixture of carbon dioxid in oxygen or air. It is therefore impossible to compare the curves of Nicloux and Henderson as they were using different percentages of carbon dioxid, but it is of interest to note that Nicloux failed to obtain marked results when using 5 per cent carbon dioxid mixtures in oxygen or air, which are the mixtures suggested for clinical use by Henderson and Haldane, respectively.

Henderson⁸ states that dogs are less sensitive to stimulation of breathing by carbon dioxid than are men, and that while 5 per cent carbon dioxid does not cause an active breathing in normal men it is sufficient to stimulate the respiratory center of persons who have been asphyxiated.

From the foregoing review it may be seen that there is a difference of opinion as to the relative value of the different treatments. An exact determination of their value would require a number of highly dangerous experiments on men, in which the percentage of hemoglobin saturated with carbon monoxid would rise as high as 65 or 70 per cent, and this is impracticable. The necessity for an exact evaluation arises

5 Haldane, J. S. The Use of Carbon Dioxid as a Remedy in Gas Poisoning, *Colliery Guardian* **128** 1633-1634 (Dec. 24) 1924.

6 Henderson, Haggard and Coburn (Footnote 2, first reference).

7 Nicloux, M., Nerson, H., Stahl, J., and Weill, J. Sur l'élimination de l'oxyde de carbone après intoxication grave: influence de la respiration de l'air ou de l'oxygène additionnée de 5 P. 100 d'acide carbonique, *Compt. rend. Soc. de biol.* **92** 178-182 (Jan. 30) 1925, Sur l'élimination de l'oxyde de carbone après intoxication grave, *ibid.* **92** 171-178 (Jan. 30) 1925.

8 Henderson, Yandell. Personal communication to authors.

from the desirability of deciding on the type of apparatus to be kept at hand. In military practice carbon monoxid asphyxia cases occur most often in military land mines or after powder explosions on war-ships. In these locations pure oxygen is usually available, in the land mines it can be obtained from the oxygen rescue apparatus kept at the pit-heads, and aboard ship from the oxy-welding outfits. Carbon dioxid is not available at these places and special supplies would have to be provided as in the "sparklet" method described by Briggs⁹ or a similar apparatus made by the Siebe Gorman Company¹⁰. If such apparatus is at hand the oxygen cylinders can be enriched with the desired percentage of carbon dioxid. Both oxygen and carbon dioxid can be easily procured in cities, and as Henderson has pointed out, any intern can quickly rig up an apparatus that will give the required mixture. In any event the weight of cylinders and apparatus required is great, and if the portable air plus carbon dioxid apparatus designed by Haldane is effective its use would be indicated in localities where transportation is difficult.

In an effort to determine the relative value of the suggested treatments the following experiments have been performed.

EXPERIMENTAL PROCEDURE

Dogs were used for the experiments. Under local anesthesia (cocain) the femoral veins were exposed, the legs bandaged and the animals were then gassed in a continuous flow gassing chamber with a rate of flow of 100 liters per minute. Pure carbon monoxid was used, introduced from a gasholder previously filled with carbon monoxid by the action of sulphuric acid on formic acid. The rates of flow and the concentrations used were controlled by flow meters.

A great divergency was noted in the behavior of the dogs, similar to that found by other observers, some dogs rapidly becoming unconscious, others showing a marked tolerance for the gas. In all cases animals were carried through the first period of rapid breathing and convulsions, then through the period of Cheyne-Stokes respiration to the point where slowing respiration indicated that the limit had been reached. Even under these conditions marked variations in the carbon monoxid hemoglobin content were found, and a number of animals were lost in spite of artificial respiration and treatment. Immediately on removal from the chamber a sample of blood was taken, and further samples were taken every ten minutes as noted in the tables. The percentage of hemo-

9 Briggs, Henry. Tr. Roy. Soc., Edinburgh, 1924.

10 This apparatus is described in *Colliery Guardian* **128** 310 (Aug. 1) 1924.

globin saturated with carbon monoxid was estimated by the pyrotannic method described by Sayers, Yant and Jones ¹¹

The control animals were placed on cradles and allowed to breathe ordinary air. The treatments on the other subjects were carried out as follows. Large cylinders were filled with the different mixtures to be used, and after twenty-four hours (to allow diffusion) samples were drawn off and analyzed to insure the proper mixture. Reducing valves were attached to the cylinders and then to a rubber hose leading to large signal corps rubber balloons. From the balloons a short length of three-fourths inch (1.87 cm) hose led to the dog face-mask. These were made by cutting off the bottoms of a number of various sized bottles to insure accurate fits, the cut end was padded and held tightly over the subject's face. The entering pipe was fitted with a check valve that prevented the exhaled air from reentering the breathing bags. A hole in the sides of the bottles contained a flutter valve, which kept the dog from inhaling air from the room. The balloons were kept well distended with the treatment mixture, so much so that there was a continual loss through the valves. This, while wasteful, assured us that the animal was receiving a sufficient supply of the mixture and was not rebreathing. The use of the smallest possible bottles as face-masks cut the factor of dead air space down to the minimum.

Ten dogs were run in each series. By adding the figures for the same time and averaging them it is possible to draw a curve that represents the average decline in carbon monoxid content of the blood under the various treatments tested. The averaging method gives the same results as several other methods that were tried and several statisticians who have examined the results state that the averaging method used is satisfactory.

PRESENTATION OF DATA

In the tables given here it is to be noted that different degrees of saturation of the blood were effected. This gives a general view of the results of treatment of cases of varied severity.

In Table 1 the individual variations in dogs without treatment is strikingly brought out and under precisely similar conditions some of the subjects eliminate carbon monoxid much faster than others.

Again the remarkable variation in rate of decrease is seen in Table 2. The average rate of decrease is of course much more rapid than in Table 1.

¹¹ Sayers, R. R., Yant, W. P., and Jones, G. W. The Pyrotannic Acid Method for the Quantitative Determination of Carbon Monoxid in the Blood, *Pub. Health Rep.* **38** 2311-2320 (Oct. 5) 1923.

TABLE 1—Rate of Elimination with No Treatment

Ex- peri- ment	Weight of Dog, Lb	Concentra- tion of Carbon Mon- oxid	Expo- sure in Min	Percentage of Hemoglobin Combined with Carbon Monoxid, at Ten Minute Intervals from End of Exposure								Remarks
				0	10	20	30	40	50	60	70	
1	23 (10.4 kg)	0.25	90	50	35	30	30	20	15	10		Respiration quiet and normal throughout
2	28 (12.7 kg)	0.25	90	50	40	30		30	20	10	10	
3	26 (11.8 kg)	0.25	105	50	50	45	40	40	35	25		
4	33 (15 kg)	0.25	95	55	45	35	25	20	15	10		On removal from chamber panting, still unconscious at 60 minutes
5	33 (15 kg)	0.25	88	65	47	40	35	35	30	30		
6	23 (10.4 kg)	0.25	65	60	50	45	35	35	25	20	20	At 10 minutes, respira- tion 76 and shallow
7	25 (11.3 kg)	0.25	80	55	50	45	30	25				
8	24 (10.9 kg)	0.25	90	65	50	40	35	30	25	15		
9	22 (10 kg)	0.25	80	55	50	50	45	40	40	30		
10	29 (13.2 kg)	0.25	75	55	45	40	40		35	30	30	At 10 minutes, respira- tion shallow, 24 per minute
Average				56	46.2	40	35	30.5	26.6	20	20	

TABLE 2—Rate of Elimination with Oxygen Treatment*

Ex- peri- ment	Weight of Dog, Lb	Concentra- tion of Carbon Mon- oxid	Expo- sure in Min	Percentage of Hemoglobin Combined with Carbon Monoxid, at Ten Minute Intervals from End of Exposure							Remarks
				0	10	20	30	40	50	60	
1	27 (12.2 kg)	0.25	85	50	30	20	10				
2	28 (12.7 kg)	0.25	90	70	45	35	30	20	10	5	Respiration 180 per minute at 10 minutes, after 50 minutes respiration 24
3	26 (11.8 kg)	0.25	40	60	35	20	20	5	5		
4	24 (10.9 kg)	0.25	75	60	45	20		10	5		Artificial respiration re- quired at first
5	26 (11.8 kg)	0.25	130	50	30	20	15	5			
6	19 (8.6 kg)	0.25	80	70	40	30	10	5			Respiration 76 on removal from chamber
7	22 (10 kg)	0.25	40	45	15	5					
8	13 (5.9 kg)	0.25	46	45	10	5					Artificial respiration at first, old dog
9	18 (8.2 kg)	0.25	110	65	45	30	20	15	10		
10	36 (16.3 kg)	0.25	58	60	35	25	15	10	10		Respiration at 0, 20 and deep
Average				57.5	33	21	17.1	10	8	5	At 10 minutes, respiration 144, shallow

* Analysis of cylinders showed oxygen 98.5 per cent

TABLE 3—Rate of Elimination with Oxygen Plus 5 Per Cent Carbon Dioxid

Ex- peri- ment	Weight of Dog, Lb	Concen- tration of Carbon Mon- oxid	Expo- sure in Min	Percentage of Hemoglobin Com- bined with Carbon Monoxid, at Ten Minute Intervals from End of Exposure						Analysis	Remarks
				0	10	20	30	40	50		
1	24 (10.9 kg)	0.25	90	45	20	5				CO ₂ =5.8 O ₂ =92.8	Respiration between 70 and 80 per minute
2	25 (11.3 kg)	0.25	110	50	25	10	2			CO ₂ =5.6 O ₂ =93.6	Respiration immediately increased when treat- ment began
3	20 (9 kg)	0.25	55	50	25	10				CO ₂ =5.6 O ₂ =93.6	
4	24 (10.9 kg)	0.25	80	50	20	20	15	5		CO ₂ =5.0 O ₂ =93.6	Artificial respiration at first
5	20 (9 kg)	0.25	105	60	25	10	5			CO ₂ =5.0 O ₂ =93.8	
6	22 (10 kg)	0.25	84	60	35	20	10			CO ₂ =5.0 O ₂ =93.8	
7	33 (15 kg)	0.25	70	60	30	15	10	5		CO ₂ =5.8 O ₂ =92.8	Fairly deep respiration
8	24 (10.9 kg)	0.25	80	55	30	15	10	5		CO ₂ =5.2 O ₂ =94.1	At 20 minutes, respira- tion 60, fairly deep
9	24 (10.9 kg)	0.25	53	65+	40	25	20	15	5	CO ₂ =4.7 O ₂ =94.5	At 10 minutes, respira- tion 82, deep, artificial needed at 0
10	28 (12.7 kg)	0.25	69	60	35	20	15		7	CO ₂ =5.8 O ₂ =92.8	At 10 minutes, respira- tion rapid and fairly deep
Average				55.5	28.5	15	10.8	7.5	6		

TABLE 4—Rate of Elimination with Oxygen Plus 10 Per Cent Carbon Dioxid

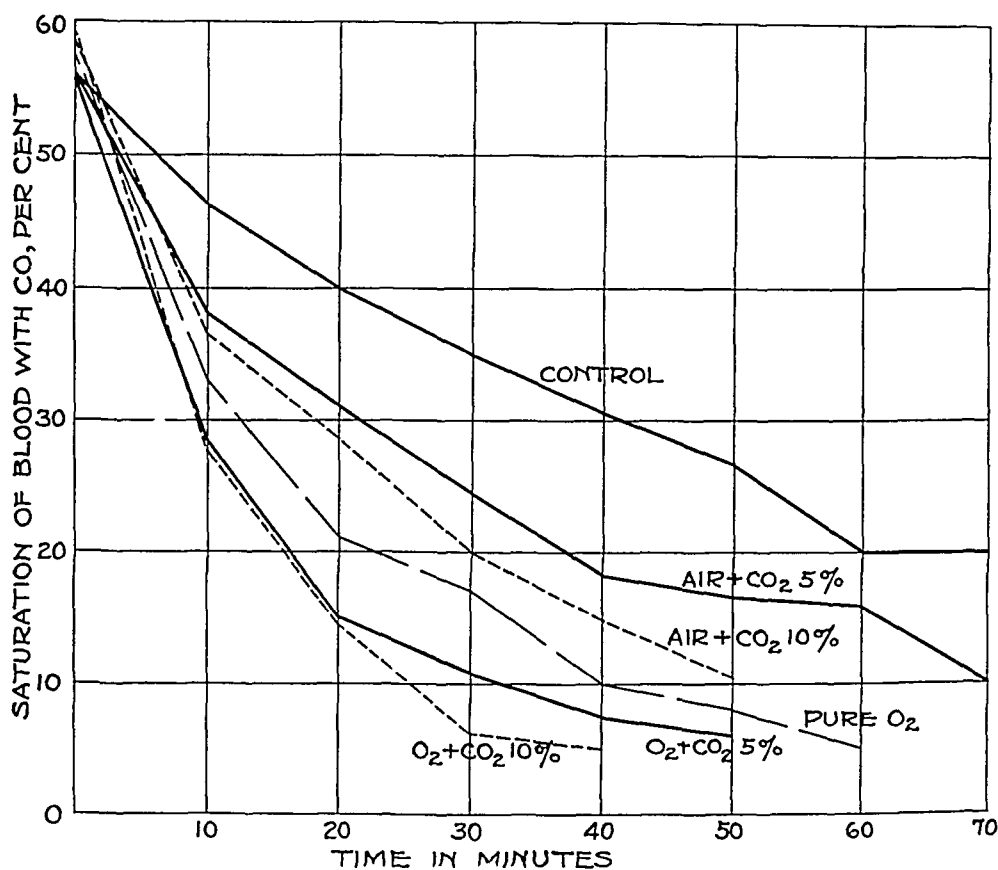
Ex- peri- ment	Weight of Dog, Lb	Concen- tration of Carbon Mon- oxid	Expo- sure in Min	Percentage of Hemoglobin Com- bined with Carbon Monoxid, at Ten Minute Intervals from End of Exposure						Analysis	Remarks
				0	10	20	30	40	50		
1	17 (7.7 kg)	0.25	60	60	20	10	5			CO ₂ =10.0 O ₂ =87.2	At 0 minute, respiration 96, at 10 minutes, 120, very deep
2	34 (15.4 kg)	0.25	75	50	25	20	5			CO ₂ =10.0 O ₂ =87.2	At 0 minute, respiration 140, at 10 minutes, res- piration 154
3	23 (10.4 kg)	0.25	61	65	27	20	10			CO ₂ =9.6 O ₂ =89.4	Breathing very hard, fast and deep
4	26 (11.8 kg)	0.25	75	60	25	10	5			CO ₂ =10.0 O ₂ =89.2	Same as Dog 3
5	26 (11.8 kg)	0.25	72	65	30	15	5			CO ₂ =9.6 O ₂ =89.4	At 10 minutes, respira- tion very deep, artifi- cial respiration at first
6	27 (12.2 kg)	0.25	70	60	30	15	5			CO ₂ =9.6 O ₂ =89.4	Respirations deep and fast
7	33 (15 kg)	0.25	85	65	30	20	10	5		CO ₂ =10.0 O ₂ =89.2	At 10 minutes, respira- tion 80, very deep and full
8	16 (7.3 kg)	0.25	85	50	40	10	7			CO ₂ =10.1 O ₂ =88.5	Respiration very deep (Second sample poor)
9	16 (7.3 kg)	0.25	90	60	30	15	5			CO ₂ =10.0 O ₂ =89.2	Respirations deep and rapid
10	17 (7.7 kg)	0.25	53	55	20	10	5			CO ₂ =10.0 O ₂ =89.2	Respiration at 10 min- utes, 60, very deep
Average				59	27.7	14.5	6.2	5			

In the series in Table 3 the rate of fall was slightly greater than in the oxygen series. The respiration of these animals was fairly deep, but no more so than that of some of the dogs treated with plain oxygen.

In the series in Table 4 the rate of elimination was even more rapid. The same individual variation in dogs was to be noted. The breathing of the animals was deep and rapid, the muscular effort involved being great.

The respiration in this series of animals, while fairly rapid and deep was less so than in the animals treated with the other mixtures.

The respirations of the animals in Table 6 was very deep and rapid.



Rapidity of fall of carbon dioxide content in blood under different treatments

DISCUSSION OF DATA

No variation was noted in the after effects of the different treatments. There was no increased tendency toward paralysis in any particular group, and it would be impossible to tell from the after history of the dogs what treatment they had received.

The individual idiosyncrasy of dogs to the gas is marked. Under similar conditions some dogs were degassed much more rapidly than others in the same group.

TABLE 5—Rate of Elimination with An Plus 5 Per Cent Carbon Dioxid

Ex- per- iment	Weight of Dog, Lb	Concen- tration of Carbon Mon- oxid	Expo- sure in Min	Percentage of Hemoglobin Com bined with Carbon Monoxid, at Ten Minute Intervals from End of Exposure										Analysis	Remarks
				0	10	20	30	40	50	60	70				
1	25 (11 3 kg)	0 25	80	70	50	50	40	35	30	25	20	CO ₂ = 5 0 O ₂ =20 2			
2	31 (14 1 kg)	0 25	90	50	40	35	30	20	15	0		CO ₂ = 5 1 O ₂ =19 7	Respirations dropped from 70 to 60, always deep		
3	29 (13 2 kg)	0 25	70	55	35	30	20	10	0			CO ₂ = 5 1 O ₂ =19 7	Respiration remained between 32 and 36		
4	25 (11 3 kg)	0 25	78	55	25	20	15	10	8	0		CO ₂ = 4 8 O ₂ =21	At 10 minutes, respi- ration 48 and deep		
5	39 (17 7 kg)	0 25	80	62	40	30	25	20	20	15	10	CO ₂ = 4 8 O ₂ =21	At 20 minutes, respi- ration 160, deep, at 40, respiration 100, fairly deep		
6	24 (10 9 kg)	0 25	80	60	45	40	30	20	15	15	10	CO ₂ = 4 9 O ₂ =20	At 10 minutes, 80, fairly deep		
7	20 (9 kg)	0 25	56	55	40	30	25	20	15	10	10	CO ₂ = 5 2 O ₂ =18	At 10 minutes, 44, deep		
8	38 (17 2 kg)	0 25	65	55	45	35	35	25	20	20	10	CO ₂ = 5 2 O ₂ =18			
9	22 (10 kg)	0 25	84	50	30	20	15		10	10		CO ₂ = 4 8 O ₂ =20	At 10 minutes, respi- ration 56, deep		
10	18 (8 2 kg)	0 25	83	47	30	20	10	5	0	0		CO ₂ = 4 8 O ₂ =20	At 10 minutes, respi- ration 80, fairly deep		
Average				55 9	38	31	24 5	18 3	16 6	15 8	10				

TABLE 6—Rate of Elimination with An Plus 10 Per Cent Carbon Dioxid

Ex- per- iment	Weight of Dog, Lb	Concen- tration of Carbon Mon- oxid	Expo- sure in Min	Percentage of Hemoglobin Com- bined with Carbon Monoxid, at Ten Minute Intervals from End of Exposure						Analysis	Remarks
				0	10	20	30	40	50		
1	25 (11 3 kg)	0 25	70	50	35	25	15	10		CO ₂ = 9 3 O ₂ =19 2	Respirations 60 per min- ute, deep and violent
2	24 (10 9 kg)	0 25	45	70	40	35	25	20	10	CO ₂ = 9 2 O ₂ =19 2	Respirations 128, deep at 10 minutes, artifi- cial respiration neces- sary
3	29 (13 2 kg)	0 25	63	55	35	30	20	15	10	CO ₂ = 9 3 O ₂ =19 2	At 0 minute respira- tions 66, fairly deep
4	40 (18 1 kg)	0 25	94	70	45	35	30	20	15	CO ₂ =10 2 O ₂ =18	At 10 minutes, respira- tions 100, very deep, at 40 minutes, deep
5	19 (8 6 kg)	0 25	100	60	40	30	25	20	15	CO ₂ =10 0 O ₂ =20 1	At 10 minutes, respira- tions 70, very deep
6	19 (8 6 kg)	0 25	64	55	35	25	15	15	5	CO ₂ =10 0 O ₂ =20 1	At 10 minutes, respira- tions 80, deep
7	22 (10 kg)	0 25	71	50	30	20	15	10	10	CO ₂ = 9 5 O ₂ =20	
8	22 (10 kg)	0 25	52	55	35	25	15	10	10	CO ₂ =10 0 O ₂ =20 1	At 10 minutes, respira- tions 60, very deep
9	34 (15 4 kg)	0 25	80	60	35	30	15	15	10	CO ₂ =10 6 O ₂ =19 8	At 10 minutes, respira- tions 60, very deep, at 30 minutes, respira- tions 48, very deep
10	25 (11 3 kg)	0 25	96	60	35	30	25	15	10	CO ₂ = 9 5 O ₂ =20	At 10 minutes, respira- tions 80, very deep, at 30 minutes, respira- tions 80, very deep
Average				58 5	36 5	28 5	20	15	10 5		

Our findings confirm the statement of Sayers⁴ that pure oxygen gives almost as rapid elimination of carbon monoxid from the blood as does the oxygen plus a 5 per cent carbon dioxid mixture. Our findings do not confirm the statement of Henderson¹ and Haldane⁵ that air plus 5 per cent carbon dioxid washes out carbon monoxid more rapidly than pure oxygen. We agree with Nicloux, Nerson, Stahl and Weill⁷ in their statement that oxygen washes out carbon monoxid more rapidly than a mixture of air and carbon dioxid, either 5 or 10 per cent.

In carbon monoxid asphyxia the period of danger is when the blood is over 30 per cent saturated with the gas. Any treatment that safely and rapidly reduces the blood saturation below this point is of value. The tables show that the rapidity of reduction by the treatments considered comes in the following order: oxygen plus 10 per cent carbon dioxid, oxygen plus 5 per cent carbon dioxid, oxygen, air plus 10 per cent carbon dioxid, air plus 5 per cent carbon dioxid.

Of these five treatments, two, the oxygen plus 10 per cent carbon dioxid and the air plus 10 per cent carbon dioxid can be dismissed at once, for there is a possible danger in their use since a weakened or diseased heart might be overtaxed by the violent respiratory efforts induced by them.

If a reduction to 25 per cent saturation of the blood be taken as a desirable point to reach as quickly as possible, an examination of the accompanying chart shows that oxygen plus 5 per cent carbon dioxid dogs reach this point in twelve and one-half minutes, oxygen dogs in sixteen and one-half minutes and air plus 5 per cent carbon dioxid dogs in twenty-nine minutes.

According to this standard, while there is but little difference in the value of the oxygen treatment and the oxygen plus 5 per cent carbon dioxid treatment, both are much superior to the air plus 5 per cent carbon dioxid treatment.

If any other point of saturation be selected as the goal to be reached as rapidly as possible, consultation of the chart will give the relative value of the treatments as regards the time required.

As compared to the untreated dogs the chart shows that all the treatments considered give a rapid rate of reduction of the carbon monoxid and a more rapid arrival of the blood at a point of saturation where any further injury to the central nervous system is not to be feared.

CONCLUSIONS

1 In dogs suffering from carbon monoxid asphyxia the difference in elimination time between oxygen treated and oxygen plus 5 per cent carbon dioxid treated subjects is slight.

2 Since the rate of elimination under pure oxygen is almost as rapid as with the oxygen plus 5 per cent carbon dioxid and since the oxygen treatment is more readily available it is recommended that its use be continued, particularly in localities where transportation is difficult

3 The air plus 5 per cent carbon dioxid treatment should be of value for rescue parties sent to inaccessible mines and especially in military operations

THE ENZYMIC ACTIVITY OF THE DUODENAL CONTENTS FOLLOWING THE INGESTION OF PANCREATIN

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The purpose of this article is to demonstrate that a pancreatin containing the three active ferments trypsin, steapsin and amylopsin, properly administered by mouth, on reaching the duodenum will retain a considerable proportion of its original enzymic activity

Long¹ has shown experimentally on dogs with Pawlow pouches that the amylopsin of a pancreatic extract is quickly reduced in activity or destroyed by the hydrochloric acid of the gastric secretion. He also noted that trypsin retained a large percentage of its activity if protected by food proteins from the digestive action of the hydrochloric acid-pepsin combination. From this he concluded that trypsin, thus protected, would unquestionably reach the duodenum and there exert its specific digestive action. There are no available studies as to the fate of lipase administered by mouth.

The studies of Long did not include an examination of the duodenal contents for pancreatic extract that had passed on into the duodenum after having been in the stomach and exposed to the action of gastric juice. He found that the retention of enzymic activity by pancreatic extract exposed to gastric secretion was inversely proportional to the length of exposure and to the p_H of the gastric juice, also that if large amounts of pancreatin were used, thereby increasing the concentration of the ferments, destruction was much less complete.

Stimulated by his work we will endeavor to show that pancreatin given in large amounts and in proper solution will pass through the stomach rapidly enough to avoid the destructive influence of the gastric juice and reach the duodenum to a large extent undestroyed.

The enzymic activities in the following experiments were determined by McClure's² methods, slightly modified, as these have been

* Presented at the annual meeting of the American Gastro-Enterological Association, May 25-26, 1925, Atlantic City, N J

* From the division of medicine, University of Buffalo Department of Medicine

1 Long, J H, and Muhleman, G W Arch Int Med **13** 314 (Feb) 1914
Long, J H, and Hull, Mary J Am Chem Soc **38** 1620, 1916, **39** 162, 1917

2 McClure, C W, Wetmore, A S, and Reynolds, L New Methods for Estimating Enzymatic Activities of Duodenal Contents of Normal Man, Arch Int Med **27** 706 (June) 1921

recognized as the most accurate and reliable that are available. Tryptic activity is expressed as milligrams of nonprotein nitrogen resulting from the digestive action of the specimen tested on a buffered casein solution. Lipolytic activity is expressed as the number of cubic centimeters of twenty-fifth normal sodium hydroxide solution necessary to neutralize the acid resulting from the digestive action of the specimen tested on a 5 per cent aqueous solution of glyceryl triacetate. Glyceryl triacetate was substituted for the cotton seed oil emulsion of McClure's method. Amylolytic activity is expressed as milligrams of glucose resulting from the digestive action of the specimen tested on a 2 per cent buffered starch solution.

The pancreatin solution used in our experiments was prepared by mixing 10 gm of pancreatin, U S P, with 200 cc of water at 10 degrees C. The three enzymes quickly pass into colloidal solution and a grayish, cloudy mixture results. This we have designated a 5 per cent pancreatin solution. It was freshly prepared and its enzymic activities determined in each experiment. Our figures show that this solution possessed approximately the same tryptic and lipolytic action as duodenal contents while its amylolytic activity was three times greater. Cold water at 10 degrees C was used in preparing the pancreatin solution as it has been shown that cold protects the enzymes from the destructive action of the gastric juice.

PROCEDURE

The duodenal tube was swallowed by a fasting subject and the tip located in the second portion of the duodenum. A specimen of fasting duodenal contents was aspirated and its enzymic activity determined. After this specimen was secured 200 cc of cold water was administered by mouth and a duodenal drip was established which persisted about fifteen minutes in each case. Specimens of this watery drip were secured at various intervals and their enzymic activities determined.

After the lapse of an hour 200 cc of the specially prepared 5 per cent pancreatin solution described above was administered orally, and in from two to five minutes produced a duodenal drip possessing all the physical characteristics of the colloidal solution ingested. In the greater number of our cases 75 per cent of the 5 per cent pancreatin solution could be recovered from the duodenum in ten minutes. Specimens of this duodenal drip were collected at one or two minute intervals until the characteristic colloidal solution could no longer be secured.

The enzymic activities of these specimens were determined and compared with the activities of the specimens secured following the ingestion of cold water. This procedure was followed as closely as possible in ten cases. Twice we administered the 5 per cent pancreatin solution forty-five minutes after a meal consisting of an egg, bread,

butter and milk, a duodenal drip again appeared and the enzymic activities of this drip were determined

The charts given here explain the results of our experimentation Chart 1 shows the enzymic activities of specimens collected after water had been administered orally, demonstrating the low activities due to water dilution Chart 2 contrasts the activities of the specimens recov-

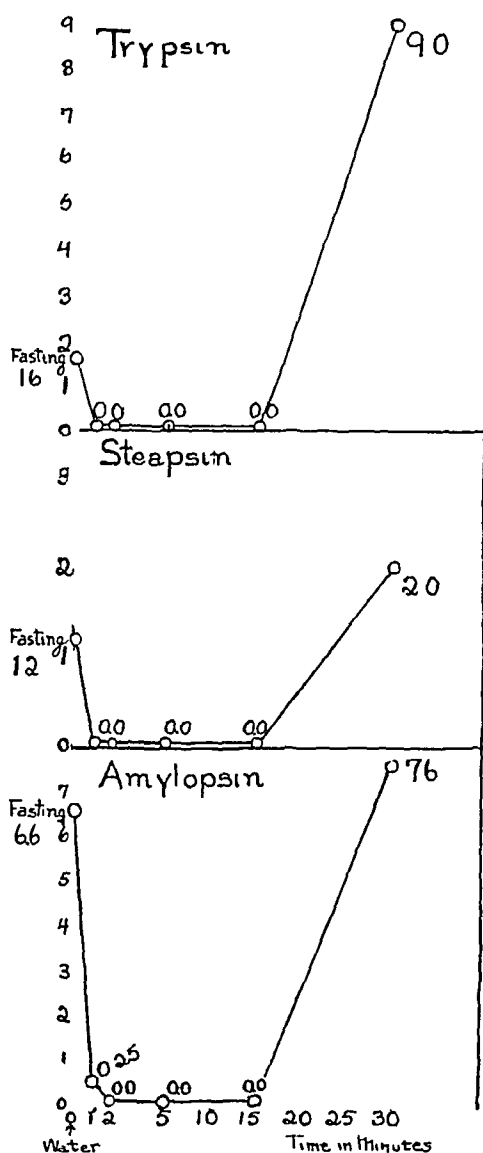


Chart 1—Typical water dilution curve showing reduction in enzymic activities over a period of fifteen minutes following the ingestion of 200 c c of cold water

ered from the duodenum after water and after 5 per cent pancreatin Chart 3 is a composite chart of our twelve cases Each figure plotted on this chart represents an average of from six to twelve enzyme determinations The enzymic activities of all the specimens we collected in our experimentation were grouped according to time intervals

after the ingestion of either the water or the 5 per cent pancreatin and an average figure calculated for each time period. The contrast between the curves on this chart is striking and presents reliable evidence that large quantities of the enzymes reached the duodenum after the ingestion of the 5 per cent pancreatin solution. It shows also that the destruction of trypsin is less rapid and less complete than that of steapsin and amyllopsin.

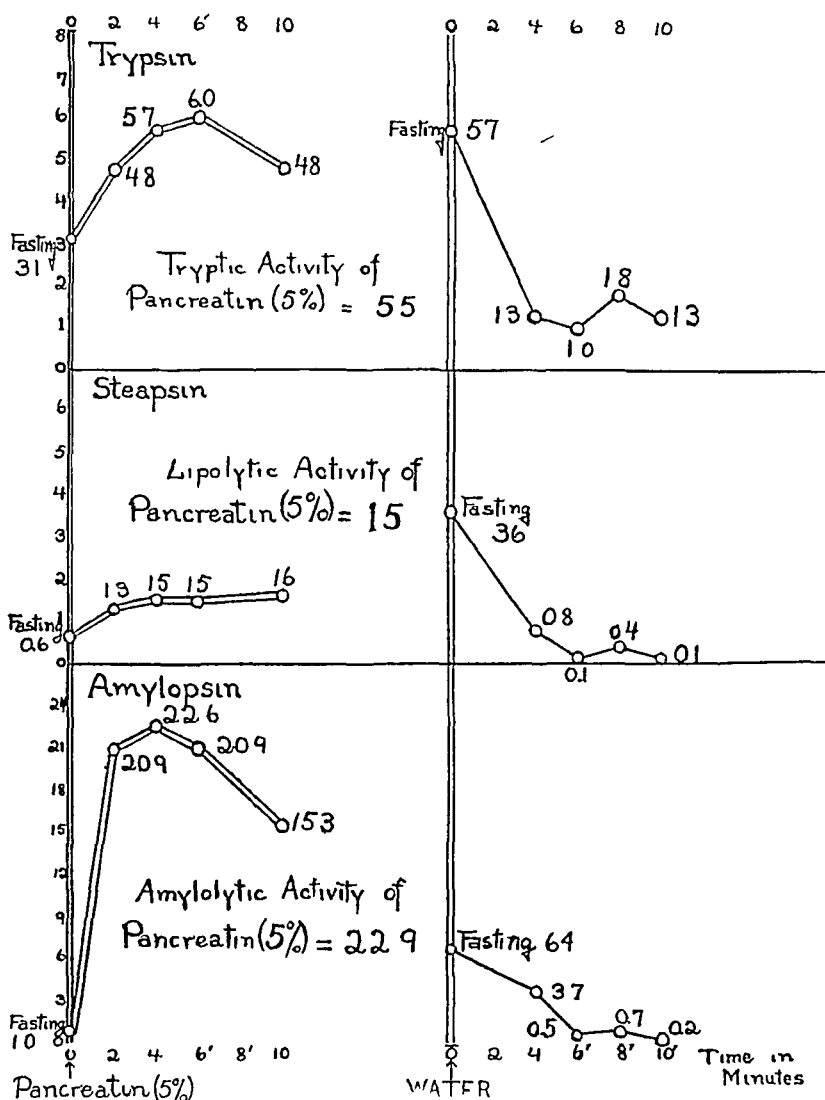


Chart 2—Water dilution curve over a period of ten minutes and curve following ingestion of 5 per cent pancreatin solution, marked rise of enzymic values following pancreatin and drop after water. The nine other cases studied in a similar manner showed the same phenomena.

SUMMARY AND CONCLUSIONS

It is possible to administer a pancreatin solution orally which will pass through the stomach and can be recovered from the duodenum by means of the duodenal tube. That this is the solution that has been administered orally is demonstrated by the fact that the specimens

collected from the duodenum possessed all the physical characteristics of that solution. We found that the 5 per cent pancreatin solution could be administered orally and portions of it could be recovered from the duodenum in from two to five minutes. Enzymic activities on specimens recovered at various times after pancreatin were much greater than those recovered in a similar manner after the ingestion of water.

The gastric contents of all the subjects studied contained free hydrochloric acid in various amounts and it was noted that in those that

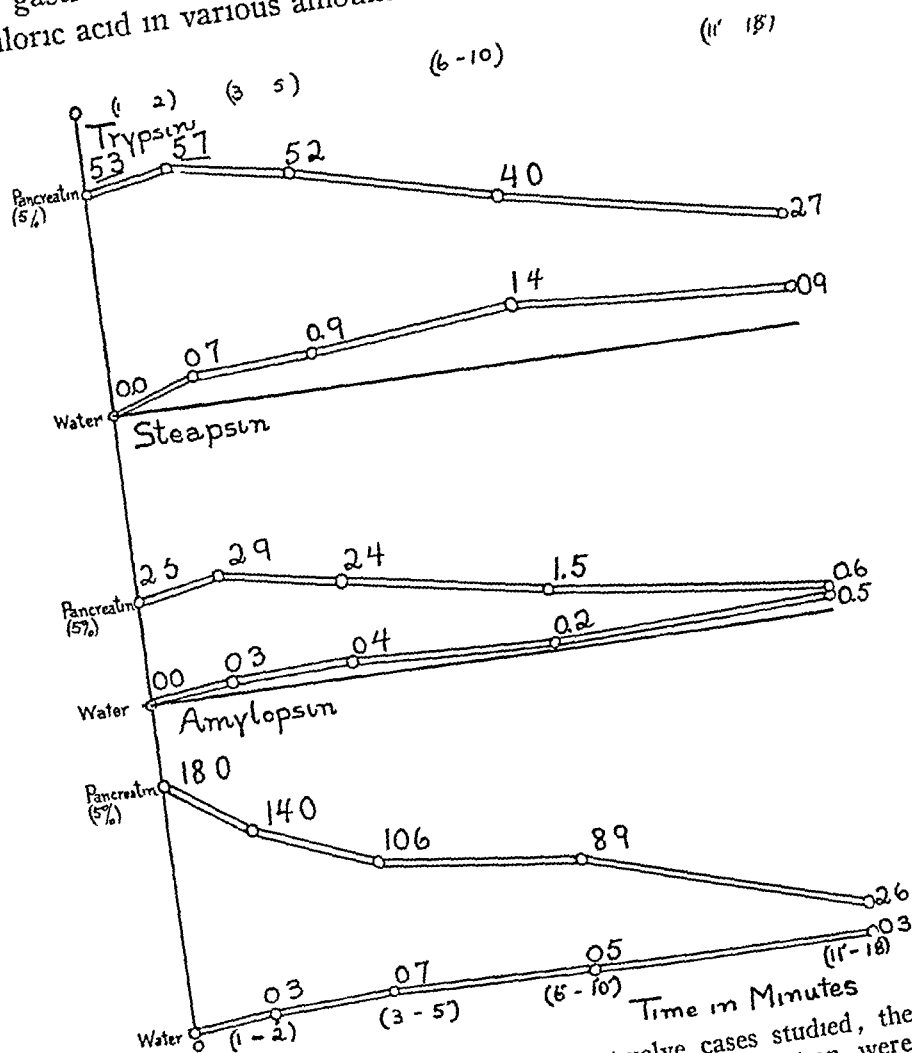


Chart 3—Water and pancreatin curves in twelve cases studied, the enzymic activities of all the specimens collected during experimentation were grouped into time intervals following the ingestion of either water or 5 per cent pancreatin solution and an average figure for each time period calculated.

tended toward hyperchlorhydria the enzymic activities were more rapidly reduced than in cases of subacidity.

We believe that it will be necessary to administer pancreatic extract containing the three ferments in cold water and in larger dosage than has been used previously, to insure its entrance into the duodenum.

undestroyed This can be accomplished by administering 5 gm of pancreatin suspended in cold water either on an empty stomach or forty-five minutes after a meal The latter fact was determined by recovering the pancreatin solution from the duodenum forty-five minutes after a meal and finding high enzymic activity therein

From our studies trypsin is least affected of the three ferments by the gastric juice, which agrees with Long's experimental findings We have also found that amylapsin and steapsin reach the duodenum to a large extent undestroyed, this being rendered possible by the rapidity with which they traverse the stomach It is difficult to estimate what portion of the enzymes thus administered do reach the duodenum undestroyed, probably most all of the trypsin and from 50 to 60 per cent of the amylapsin and steapsin in the average case

No conclusive study of the clinical effects of enzymes thus orally administered has been made and no opinion will be expressed on this problem However, we conclude from our experiments that a properly prepared and ingested pancreatin solution will pass through the stomach rapidly enough to insure the retention of a considerable portion of its original proteolytic, lipolytic and amylolytic activity when it reaches the duodenum

THE RELATION OF THROMBOCYTES TO HEMORRHAGIC DIATHESIS

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The clinical study of thrombocytes is rapidly gaining recognition not only in diseases connected with the hematopoietic system but also in infectious and metabolic disorders Stahl¹ and others have recently pointed out the importance that the number, the size and the staining of the thrombocytes play in the diagnosis and prognosis of various diseases This discussion will be confined chiefly to the rôle played by the thrombocytes in hemorrhagic diathesis

For a long time the thrombocytes had been considered as imperfect or deformed red cells, that is, the débris of red blood cells In 1877 Hayem described thrombocytes under the name of hematoblasts because he believed these structures to be youthful forms of red blood cells In 1881 Brohm observed two cases of Werlhoff's disease and was the first to point out that in this affection the hematoblasts were markedly diminished

In 1883 Krauss,² in the clinic of Brohm in his dissertation on Werlhoff's disease, pointed out that the hematoblasts are markedly diminished during the height of the disease and that they reappear when the hemorrhages disappear If Krauss had been familiar with the contribution of Bizzozero,³ who a year previous described hematoblasts under the name of blood platelets and designated them as a third independent formed element of the blood, and stated that the aggregation of the blood platelets is the underlying foundation of every thrombus, Krauss would have correlated more closely the bleeding with the diminution of blood platelets Brohm attributed the disease to a breaking up of the hematoblasts and their deleterious effect on the blood vessels Denys,⁴ the Belgian pathologist, working independently found that the blood platelets are diminished in certain diseases accompanied by hemorrhage It remained for Duke⁵ in this country in 1910 to point out emphatically and conclusively that the hemorrhages in Werlhoff's purpura are due to a diminution of the blood platelets Based on extensive clinical material and experimental studies that consisted in diminishing the number of blood platelets in the rabbit by injections of diphtheria antitoxin or

1 Stahl, R Ztschr f ang Anat Festschrift fur Martius 6 301-319, 1920, Ztschr f klin Med 96 182-211 (Jan) 1923

2 Krauss, E Ueber Purpura, Inaugural Dissertation, Heidelberg, 1883

3 Bizzozero Virchows Arch f path Anat 90 251, 1882

4 Denys Zentralbl f allg Path u path Anat, 1893

5 Duke, W W J A M A 55 1185 (Oct 1) 1910, J Exper Med 14 265, 1911, Arch Int Med 10 445 (Nov) 1912

benzene, he found that if the blood platelets were diminished below 35,000 to the cubic millimeter, hemorrhages resulted which disappeared after they increased in number. The blood platelets also can be made to disappear from the blood by injections of peptone, gelatin and colloid. Even if they do not disappear after the injection of such substances, they lose their thrombus forming ability. Lee and Robertson⁶ caused a diminution of blood platelets in rabbits by injections of antiplatelet serum. Duke emphasized the difference between the coagulation time and the bleeding time and proved that the prolonged bleeding time is caused by a diminution in blood platelets. Hayem recognized the fact that the retractability of the blood clot is influenced by the blood platelets. In fact the recent studies of Frank,⁷ Kaznelson,⁸ Keisman,⁹ Brill and Rosenthal¹⁰ are due to the stimulating and brilliant work of Duke.

It is now a universally accepted fact that the blood platelets are independent elements of the blood. Normally, they number 300,000 or 350,000 to the cubic millimeter if counted according to the method of Hayem, but according to Pratt's¹¹ method, they total 469,000 to the cubic millimeter. They are uniform in size, from 2 to 4 microns in diameter. Wright¹² showed that they are derived from the megakaryocytes of the bone marrow, that they reach the circulating blood by budding off from the mother cell, and that they possess ameboid movement. They never leave the blood stream as is the case with the red and white blood cells. This explains why the blood platelets are never found in lymph, serous cavities or purulent collections. They are at times found in large numbers in the spleen, where they are normally destroyed. If the blood is allowed to flow from blood vessels the blood platelets break down readily. This is generally attributed to the fact that they lose their carbon dioxide. They are the only elements in the blood in which thrombogen has been demonstrated, this accounts for its property of thrombus formation. Frank terms the blood platelets thrombocytes because of this ability. Duke as well as Minot¹³ and Frank demonstrated conclusively that if the thrombocytes in the blood are reduced below 50,000 even slight trauma causes ecchymosis. On this fact is based the capillary stasis test (Rumpel-Leede), also known as the capillary resistance test.¹⁴

6 Lee, R. I., and Robertson, O. H. *J. M. Res.* **33** 323 (Jan.) 1916

7 Frank, E. *Ergebn. d. ges. Med.* **3** 171-211, 1922

8 Kaznelson, P. *Ztschr. f. klin. Med.* **87** 88

9 Keisman, M. *Med. Klin.*, January, 1922, No. 3

10 Brill, N. E., and Rosenthal, N. *Am. J. M. Sc.* **166** 503 (Dec.) 1923, *Arch. Int. Med.* **32** 939-953 (Dec.) 1923

11 Pratt, J. H. *Osler and McRae Modern Medicine* **4** 694, 1915

12 Wright, J. H. *Boston M. & S. J.* **154** 643, 1906, *Virchows Arch. f. path. Anat.* **186** 55, 1906

13 Minot, *Am. J. M. Sc.* **152** 48 (July) 1916

14 Hess, A. F. *Hemophilia*, *Arch. Int. Med.* **17** 203 (Feb.) 1910

According to Bordet,¹⁵ the thrombocytes furnish a cytozyme that causes the formation of a blood clot. Stahl demonstrated that morphologically two types of thrombocytes may be encountered even in healthy persons, namely, the neutrophilic giant thrombocyte and the basophilic giant thrombocyte, the former once found is always present, the latter is only occasionally encountered and is more frequent in disease. They are the direct consequence of irritation of the megakaryocytes and are, in reality, the immature or youthful thrombocytes. These immature forms may sometimes be small or of medium size.

A slowing up of the blood stream causes the thrombocytes to adhere to the zone of the vessels and is thus responsible for thrombosis *intra vitam* in cases of circulatory weakness. Wherever there is a foreign body in the tissues, the thrombocytes collect around it. They have an agglutinative property by virtue of which they rapidly adhere to cut or injured surfaces of tissues, this results in the formation of a thrombus. The minimum number of thrombocytes necessary for this adhesive property is low compared to the number of blood platelets encountered in the essential thrombocytopenic state. Their agglutinative power also explains the retractile property of the blood clot and the presence of a nonretractile blood clot if the thrombocytes are greatly diminished. They have neither nuclei nor definite shape. It was recently demonstrated why they increase in number, size and in basophilic granules in many infectious diseases. It has also been shown by Onaka that they consume much oxygen.

Hemorrhagic diathesis characterized by a marked reduction of thrombocytes in the blood has been termed by Frank thrombopenia and by Eppinger thrombocytopenia. In view of the unknown etiology of this disease, it is termed essential thrombopenia or essential thrombocytopenia.

Thrombocytopenia has clinical manifestations similar to hemophilia except that in hemophilia the coagulation time is prolonged and the bleeding is never spontaneous. In hemophilia, cytozyme is diminished according to Bordet, hence the delay in coagulation time. In thrombocytopenia, cytozyme is normal. In essential thrombocytopenia, cytozyme is rapidly formed, but the amount is diminished on account of the presence of fewer thrombocytes, which cause prolonged bleeding. The citrated clear purpuric plasma does not clot even after standing several hours, undoubtedly owing to the sedimentation of the thrombocytes.

An increase in thrombocytes is present in few diseases, such as chlorosis, secondary anemia, polycythemia rubra, megalosplenica (Vaquez) and, at times, in lymphatic leukemia.

15 Bordet, J. *Bull. Johns Hopkins Hosp.* 32:213 (July) 1921.

CLINICAL ASPECTS WERLHOFF'S DISEASE

In 1740 Werlhoff described a symptom complex under the name *morbus maculosus hemorrhagica* characterized by spontaneous hemorrhages from the mucous membranes and by the appearance of petechiae or ecchymosis under the skin. He states that the disease may occur in both sexes during all periods of life, but is somewhat more frequent in early adult life. It may run a course of varying severity but as a rule has no tendency to recur. At times the hemorrhages from the internal organs are so severe as to cause marked secondary anemia, so that a fatal outcome may seem inevitable when sudden recession of the symptoms with subsequent complete recovery occurs. A fatal termination is rare. In some cases the hemorrhages occur only from the internal organs, the gastro-intestinal tract, or from the kidneys and, more rarely, in the form of pulmonary hemorrhages. Hemorrhages into the pleura and pericardium may take place. Hemorrhages into the peritoneum are exceedingly rare. The disease runs an afebrile course or, at most, has a moderate elevation of temperature. Sometimes the temperature runs fairly high due to the absorption of blood from the hemorrhagic areas or to a secondary infection. The secondary infection may take place from the mouth, especially from the gums and the tonsils, already devitalized and ulcerated owing to the excessive loss of blood. The disease is neither constitutional nor hereditary, nor does it generally affect more than one member of the same family.

The symptomatology as described by Werlhoff can hardly be modified. A number of important facts have been added to the study of this disease. It has been proved that one of its main characteristics is the primary reduction in the number of thrombocytes, hence the name, essential thrombopenia (Frank) or essential thrombocytopenia (Eppinger). Fonio's¹⁶ method for blood platelet count is advocated. The finger tip is cleansed with alcohol, then a drop of 14 per cent magnesium sulphate solution is placed on it. A drop of blood is obtained from the finger tip covered with the applied solution. This causes the drop of blood to mix with the magnesium sulphate. A smear is then made and stained deeply with Giemsa solution. The thrombocytes appear isolated, both the erythrocytes and the blood platelets are counted. Only 1,000 red cells are counted and the number of erythrocytes to the cubic millimeter is determined. It is simple to calculate the number of thrombocytes. There is one thrombocyte to fifteen or twenty erythrocytes.

The prolongation of bleeding time is another important diagnostic sign in thrombocytopenia and is carried out as follows according to

16 Fonio. Cor-BI f schweiz, Aerzte 45 1505, 1915

Duke's method The lobe of the ear is punctured Normally, the blood oozes from one to three minutes In thrombocytopenia it is prolonged as long as ten minutes or even for hours

The decrease in the number of thrombocytes is also responsible for the diagnostic sign described by Hayem, namely, the failure of the clot to retract Glanzman¹⁷ attributed this failure to some defect of the thrombocytes and called the condition thrombo-asthenia Brill and Rosenthal pointed out that in thrombocytopenia before splenectomy, even if the thrombocytes increase to 80,000, the clot fails to retract, according to Brill and Rosenthal this signifies that the spleen in this disease counteracts the retractability of the blood clot The coagulation time is usually not interfered with in this disease

Another important diagnostic sign is the capillary resistance test (Rumpel-Leede, A F Hess) This depends both on the diminution of thrombocytes and the associated condition of the blood vessels in this disease A tourniquet is applied to the arm from one to four minutes, tight enough to prevent the return circulation without obliterating the pulse According to the degree of hemorrhagic diathesis, petechiae or even large ecchymotic areas appear on the forearm The tourniquet should not be applied longer than five minutes because in that case petechiae would occur even in normal persons

CLINICAL SUBDIVISIONS

According to the severity of the disease and according to its cause, Frank subdivides essential thrombocytopenia into benign and malignant forms The benign form runs a clinical course corresponding to the mild type described by Werlhoff The blood picture shows a reduction in the number of thrombocytes This benign form may recur and cause a moderate degree of secondary anemia of the chlorosis type, in which the hemoglobin may be reduced out of proportion to the red blood cells The latter show considerable vacuolization and moderate anisocytosis and poikilocytosis The leukocytes are unaltered except that sometimes the mononuclears predominate or, occasionally, a few immature white cells are found With the subsidence of the symptoms the blood picture rapidly returns to normal The thrombocytes never return to their normal number If the recurrent type of thrombocytopenia is continued over a long period of time, it may bring about a condition simulating hemophilia in which petechiae, ecchymosis and mild mucous membrane hemorrhages either are spontaneous or appear on slight trauma This condition Frank terms pseudohemophilia The coagulation time is delayed, but not to the same degree as in true hemophilia, which occurs exclusively, as is well known, in the male

Cases of chronic recurrent thrombocytopenia with the manifestations of pseudohemophilia must be differentiated from true hemophilia. True hemophilia is a hereditary abnormality of the blood or hematopoietic organs limited to males but transmitted by the females. It is characterized by a deficiency of prothrombin and cytozyme (Bordet) in the blood which causes a delay in coagulation and exposes the patient to fatal hemorrhage. It usually occurs much earlier in life than thrombocytopenia. It is often encountered in the first year of life. It is interesting to know that the umbilicus at birth is rarely a site of hemorrhage in hemophilia. Circumcision, on the other hand, may be the cause of fatal hemorrhage. In fact, piercing of the ears, snipping of the frenum of the tongue or circumcision may for the first time reveal the presence of the disease. The hemorrhages, wherever they occur, are preceded by trauma. The tendency to bleed varies in intensity at different times according to the state of coagulability of the blood at that particular time. At one time a slight trauma may result in severe hemorrhage, while at another time, even a severe trauma, may only cause slight ecchymosis. In the severe cases the joints are markedly affected, and if so, the hemorrhages usually reach the periosteum and the bone proper with consequent hemorrhagic periosteitis and osteitis. According to the studies of McLean,¹⁸ the anticoagulation action of the blood in this disease has been experimentally demonstrated to be due to the action of the two phosphatids, one of which is isolated from the heart muscle and the other from the liver. If these phosphatids are added to normal blood *in vitro* or *in vivo*, a decrease in the amount of prothrombin results together with an increase in the antithrombin. The injection of phosphatid into the circulation of dogs causes hemophilic manifestations. According to Eddis,¹⁹ there is a qualitative defect in the prothrombin in this disease. The important differentiating points between hemophilia and thrombocytopenia are: The former occurs exclusively in males with characteristic hemorrhages into the joints, it is hereditary, it has a delay in coagulation time and a delay in prothrombin time, a normal number of thrombocytes and a normal bleeding time with the normal retractable blood clot.

The differential diagnosis of scurvy may at times come into consideration. This disease as it is now universally accepted is primarily a deficiency disease and the symptoms are the result of avitaminosis. If food, such as green vegetables, fruit juices, potatoes and raw milk, is added to the diet of those afflicted with scurvy, the symptoms rapidly disappear. In this affection the hemorrhages are more marked in the gums and around the hair follicles. In adults they are more marked in the muscles of the calf, and in children the joints (Moller-Barlow's

18 McLean, Jay. *Am J Physiol* **41** 250 (Aug) 1916

19 Eddis. *Proc Soc Exper Biol & Med* **14** 19, 1916-1917

disease) are more often affected. The coagulation time and bleeding time are not interfered with and the thrombocytes are normal in number. According to Matthes,²⁰ the skin in scurvy has a grater-like roughness and the gums are not as frequently affected as is stated by Littens. The disease is often preceded by rheumatic pains, general malaise and pain in the gums. If the disease is recognized during this stage and proper treatment instituted, the hemorrhages into the gums do not occur. Bleeding from the gums occurs only where the teeth are present. The same author also states that during the World War, hemorrhagic effusion into the pleura was frequently encountered in scurvy. Selle and Rosenberg,²¹ who contributed an excellent treatise on scurvy, state that adults afflicted with scurvy have a tendency to walk on the tips of the toes and present the jumping-jack phenomenon.

MALIGNANT TYPE OF THROMBOCYTOPENIA

The malignant type is that in which the hemorrhages from the internal organs with marked ulceration of the mouth, tonsils and pharynx occur, the petechiae are less marked. The anemia is marked. Hemoglobin may be as low as 30 per cent, and in some cases as low even as 20 per cent. Not only are the thrombocytes reduced to a minimum and, sometimes, even completely absent, but the red cells are considerably reduced in number. They show marked poikilocytosis and anisocytosis and Howell-Jolly bodies as well as Cabot's rings—a sign of marked destruction of the red blood cells. Leukopenia as low as from 1,500 to 2,000 to the cubic millimeter, with a diminution or complete disappearance of neutrophils, a replacement of neutrophils with lymphocytes and also the disappearance of eosinophils is encountered. In malignant thrombocytopenia not only are the megakaryocytes affected but the erythropoietic and myelocytic element of the bone marrow as well. Because of the leukopenia Frank terms this condition aleukia. This term does not seem justifiable because it signifies only that the leukocytes are diminished while in reality the red blood cells and thrombocytes are equally altered. Furthermore, the term aleukia often leads to a confusion of the condition with subleukemic or aleukemic leukemia, diseases from which it must be carefully differentiated, from both the prognostic and the therapeutic standpoints. It is therefore much more advisable to adhere to the term malignant thrombocytopenia. The term malignant does not signify that the condition is invariably fatal, for patients have recovered spontaneously or after appropriate treatment. It is malignant from the standpoint of symptomatology.

20 Matthes. *Differential Diagnosis*, translated by Held and Gross, Philadelphia, 1925, pp. 114 and 327.

21 Selle and Rosenberg. *Ergebn d inn Med u Kinderh* **19**, 1921.

Malignant thrombocytopenia must be differentiated from the following conditions subleukemic and aleukemic leukemia, of both the lymphatic and the myeloblastic types, sepsis and agranulocytic angina

The acute type of aleukemic leukemia of the lymphatic types sets in with high temperature, ulceration of the gums and pharynx, and necrosis of the tonsils that may simulate Vincent's angina or severe diphtheric destruction of the tonsils. The petechiae are scattered throughout the body. There usually is enlargement of the lymphatic glands and enlargement of the spleen. The thrombocytes usually are not diminished in number and are sometimes even increased. The bleeding time is not interfered with and the retractability of the blood clot is firm. The chronic type of lymphatic leukemia is so different in its symptomatology from thrombocytopenia that the differential diagnosis does not enter into consideration.

The acute aleukemic and subleukemic types of myeloblastic leukemia do not, as a rule, show the same hemorrhagic manifestations as does thrombocytopenia. The spleen usually is enlarged in these cases. The thrombocytes are only moderately reduced in number in proportion to the anemia. The bleeding time is normal and the retractability of the blood clot is firm. The myeloblasts and the myelocytes give a positive oxydase reaction. It is also important to remember that either form of acute leukemia may set in gradually and that the active symptoms may be preceded by pain in the gums which causes the patient to consult a dentist who extracts one or more teeth. The severe systemic symptoms that follow are then attributed to the extraction, and the dentist often is innocently sued for malpractice.

APLASTIC ANEMIA

Another disease with which the symptoms of thrombocytopenia has much in common is aplastic anemia. Aplastic anemia is a term introduced by Ehrlich, who observed a case of pernicious anemia in which the normoblasts disappeared from the blood and the color index became low. He predicted that there would be rapid fatal termination of this case, as the blood showed that the regenerative power of the bone marrow had disappeared. He also predicted that the bone marrow of the long bones would be yellow instead of red because of the absence of regenerative power of the bone marrow. The necropsy proved this assumption to be correct. Ehrlich therefore reserved the use of the term aplastic anemia to the terminal stage of pernicious anemia, or to those cases of pernicious anemia that run a fulminating fatal course without showing any regenerative power on the part of the bone marrow. For a time both clinicians and hematologists accepted Ehrlich's view with regard to aplastic anemia. As cases of anemia with absence of regenerative power of the bone marrow began to

accumulate without any evidence of pernicious anemia, clinicians and hematologists considered aplastic anemia as an independent clinical picture. According to Eppinger, the disease sets in acutely in the midst of perfect health, with hemorrhages from the internal organs, often from the uterus. Sometimes there is severe epistaxis. At times the continuous oozing of blood rapidly leads to severe secondary anemia, and quite often there is a reduction in leukocytes. Not infrequently the thrombocytes also are diminished in number, the disease then resembling malignant thrombocytopenia. It is sometimes difficult to differentiate the disease from thrombocytopenia, as in some cases petechiae are also present. In contradistinction to pernicious anemia, the subicteric tinge of the skin and of the sclerae is absent in aplastic anemia. This fact was noted by Turck and confirmed by Eppinger. These two authors also pointed out that urobilinuria—an important factor in pernicious anemia—is not so pronounced in aplastic anemia. Both phenomena, that is, the absence of subicteric tinge of the skin and of the sclerae together with the absence of urobilinuria, indicate that the process of blood destruction is not the same in pernicious as in aplastic anemia. Further proof that in aplastic anemia the destruction of the blood is of different nature from that in pernicious anemia is brought by Eppinger in a case studied both clinically and pathologically. Clinically, he found normal acidity of the stomach, no urobilin in the urine, no increase of bilirubin in the blood, a normal output of iron in the stool—it differed in every respect from the destruction of pernicious anemia. The post-mortem findings showed sulphur yellow bone marrow of the long bones, but no hemosiderosis in the liver or in the spleen. Wallgren's²² experience, based on clinical and pathologic studies, confirms Eppinger's findings. Another important differentiating point between pernicious and aplastic anemia is the fact that in the latter there are never any changes of subacute combined degeneration of the spinal cord, as is so often the case in the former. It must therefore be accepted that aplastic anemia is a clinical entity that may occur in the course of pernicious anemia or secondary to severe hemorrhages or often may appear without any known cause, as does essential thrombocytopenia. The differential diagnosis between aplastic disease and essential thrombocytopenia would, under such conditions, be impossible.

Severe sepsis, especially of streptococcic or staphylococcic origin, may sometimes run a course simulating malignant thrombocytopenia. The blood picture in sepsis, however, is that the polymorphonuclear cells are markedly increased even if there is a leukopenia. The repeated chills as well as the marked delirium also are factors aiding in the differential

²² Wallgren, Ivor. *Arb a d Path Inst d Univ Helsingfors*, 1925, pp 275, 366

diagnosis Severe hemorrhages such as are encountered in malignant thrombocytopenia are rare in sepsis

AGRANULOCYTIC ANGINA

In 1922 Schultz and Verse²³ and Friedeman²⁴ and, soon after, Leon²⁵ described a clinical picture under the name angina agranulocytica, occurring usually in middle aged women, which was attributed to an intoxication or an infection It has an acute onset, with high temperature, necrosis of the mucous membrane of the mouth and pharynx, marked leukopenia and absence of neutrophilic leukocytes This disease terminates fatally At the necropsy the liver and the spleen are normal but the bone marrow shows marked pathologic changes A number of cases have since been reported Skiles²⁶ described a case fully under the term agranulocytic angina, and Piette²⁷ studied the histopathology of a similar case The last named author, in contradistinction to the others, found that the structure of the spleen was markedly changed and that there was enormous development of the sinus endothelial system at the expense of the lymphatic tissue The endothelial cells comprised about 90 per cent of the entire splenic substance The sinuses appeared empty in most places but in some places they contained mycotic emboli, a few lymphocytes and an occasional plasma cell Not a single polymorphonuclear cell was to be seen either in the spleen or in any other organ In the capsule of the spleen and of the liver numerous bacilli were present In some of the capillaries, bacterial emboli were encountered, a condition common in practically all forms of sepsis The most pronounced changes were in the kidney Innumerable bacterial emboli were distributed over the cortex and were particularly abundant in the region of the vas afferens and in the glomeruli, but without any inflammatory reaction The suprarenal glands also contained numerous emboli in the capsules of the cortical substances without any evidence of inflammation The remaining organs showed areas of superficial necrosis In view of the fact that numerous bacilli were found in the various organs, Piette asserts that the disease is of bacillary origin and is possibly due to *Bacillus pyocyaneus* Whether the term agranulocytic angina should be used for a distinct disease or merely as the expression of severe sepsis is still unsettled It resembles malignant thrombocytopenia in its mouth lesions, in the marked secon-

23 Schultz and Verse *Deutsch med Wchnschr*, 1922, No 44

24 Friedeman, U *Med Klin*, No 41, 1922-1923

25 Leon, A *Deutsch Arch f klin Med* **143** 118 (Aug) 1923

26 Skiles, J H *Agranulocytic Angina*, *J A M A* **84** 364 (Jan 31) 1925

27 Piette, E C *Histopathology of Agranulocytic Angina*, *J A M A* **84** 1415 (May 9) 1925

dary anemia, and especially in the disappearance of polymorphonuclears and eosinophils from the blood. It differs from essential thrombocytopenia by the fact that there is but slight if any diminution in thrombocytes, by the absence of petechiae or hemorrhages from internal organs and by the normal bleeding time and the normal retractability of the blood clot.

PATHOGENESIS

The question is still unsettled as to the true cause of the sudden reduction of thrombocytes in thrombocytopenia.

Kaznelson believes that the thrombolytic action of the spleen is the primary factor, he bases his assertion on the fact that in thrombocytopenia the removal of the spleen has a curative effect and that in some cases the spleen is enlarged. Kaznelson also asserts that in these cases a marked increase in destroyed blood platelets is found in the sinuses of the removed spleen. While it is true that splenectomy exercises a beneficial effect on the symptoms of thrombocytopenia, it by no means brings about a cure. The bleeding as well as the retractile property of the blood clot returns to normal, the number of thrombocytes increases only temporarily and within a few weeks again reaches the point it was before the operation, sometimes it does this a few days after the operation. The disappearance of the hemorrhages after splenectomy would indicate, according to Brill and Rosenthal, that an agency is present in the normal spleen which has some controlling mechanism on the capillary activity through the medium of the blood platelets.

The fact that the bleeding ceases even in the presence of a diminished number of thrombocytes after splenectomy in this disease would also show, according to these authors, that normally the spleen influences the two important properties of the thrombocytes, namely, the one that produces blood retraction and the agglutinative power to form thrombi. These properties may be restored immediately after the removal of the spleen or by a later steady development. The process involved is therefore not due to the spleen exercising an inhibitory or destructive property on the megakaryocyte but to the harmful influence of the reticulo-endothelial system on the thrombocyte.

Another proof that the spleen is not the primary cause of thrombocytopenia is the fact that most observers fail to find an increase of destroyed thrombocytes in the sinuses of the removed spleen. In reality there is a decrease of these elements. Klempeier, in a personal communication, said that he had studied a number of such spleens in the Postgraduate Pathological Laboratory, and found this organ absolutely normal. The cases quoted by Kaznelson and Keisman, in which the spleen was enlarged with an increase in destroyed thrombocytes in the

sinuses, in all probability belong to symptomatic purpura secondary to splenomegalic disease

Frank is of the opinion that the primary factor is the failure of the megakaryocyte to produce a sufficient number of thrombocytes. Most authors, including Eppinger and Christian,²⁸ adhere to that theory.

It seems reasonable to assume that in essential thrombocytopenia due to some unknown toxin of infectious, chemical or metabolic nature, the megakaryocytes become affected and thereby produce an insufficient number of thrombocytes of an inferior quality. The normal number of thrombocytes is undoubtedly in excess and serves the purpose of reserve. The severity of disease of any organ depends on the rapidity with which the reserve is used up. In the case of essential thrombocytopenia the reserve is quickly exhausted because of diminished production by the megakaryocyte and the destructive action of the spleen. It cannot be definitely stated whether the inhibitory factor lies in the spleen alone or in the entire reticulo-endothelial system. In view of the fact that shortly after the removal of the spleen the thrombocytes are again reduced and sometimes some of the symptoms recur is a proof, as stated by Bill and Rosenthal, that the remaining reticulo-endothelial system may also exert a detrimental effect on the megakaryocyte. It is of the utmost clinical and therapeutic importance in every disease to trace the lesion to its original source. In cardiac disease, for instance, the diagnosis would be incomplete unless one localized the affection either in valve or heart muscle. Diseases affecting the hematopoietic system must likewise be traced to the original source, although the symptoms may be similar irrespective of where the primary affection lies. If the erythroblastic elements are primarily affected, polycythemia or pernicious anemia results, the affection of the mother cell of the leukocyte is responsible for leukemia, and the affection of the mother cell of the thrombocyte causes thrombocytopenia and, in rare cases, an increase in thrombocytes. Although one of the three named mother cells may be first affected, it is self understood that the others become coaffected in the course of time, and that eventually the entire hematopoietic system becomes involved. This explains why in pernicious anemia there are eventually associated changes in leukocytes and thrombocytes. Leukemia in turn affects the erythrocytes and thrombocytes, thrombocytopenia in the benign form affects mainly the blood platelets, but in the severer form the erythrocytes and leukocytes are likewise affected, bringing about a marked reduction in polymorphonuclear leukocytes, absolute absence of eosinophils and a great reduction in red blood cells.

A primary disease of the hemolymph glands or of the liver, in the course of time, brings about pathologic changes in the hematopoietic

part of the bone marrow Lymphogranuloma, for instance, causes a reduction in red blood cells as well as marked leukocytosis and mononucleosis Splenomegalic anemia eventually affects the hematopoietic quality of the bone marrow, bringing about mononucleosis and severe anemia and mucous membrane hemorrhages

SYMPTOMATIC PURPURA

In contradistinction to primary essential thrombocytopenia, other forms of hemorrhagic diathesis, with reduction in blood platelets or without such reduction, should be termed secondary purpura or symptomatic purpura The two most important diseases of this group are those described by Schoenlein and by Henoch These two diseases are also known as hemorrhagic capillary toxicosis or anaphylactoid purpura The main characteristics of these diseases are the pathologic changes in the capillaries

SCHOENLEIN'S PURPURA

The following clinical manifestations are present in Schoenlein's purpura edema and swelling of the joints, purpuric spots of varying sizes, at first bright red in color and later dark, appearing mostly on the lower extremities The purpuric spots show a marked tendency to appear in groups and to recur The duration of the disease is from one to six weeks After the disappearance of the purpura, if the patient is out of bed there may be a rapid recurrence Schoenlein states that the petechiae are principally confined to the areas around the ankles, and that they are never larger than a pea It is well known, however, that the petechiae may occur over other parts of the body, especially over the extensor and the flexor surfaces of the extremities, and that they may at times be as large as an urticarial wheel or take the form of circumscribed erythema The hemorrhagic areas are surrounded by a red zone and sometimes by hemorrhagic nodules resembling erythema nodosum The disease is also named rheumatic peliosis Ottenberg²⁹ rightfully states that this term should not be used because it gives the erroneous impression that the disease is allied to acute articular rheumatism In reality, as Ottenberg pointed out, it has nothing in common with polyarticular rheumatism It is never preceded by tonsillitis, never favorably influenced by salicylates, it is never complicated by endocarditis nor do the joint affections ever become chronic Unlike polyarticular rheumatism, it is not hereditary nor familial The capillary stasis test is usually positive in Schoenlein's disease and negative in polyarticular rheumatism The positive test is not due to the diminution of the platelets because they are normal in number in this disease, but to the diseased state of the capillaries There is never leukocytosis in

Schoenlein's purpura, while in polyarticular rheumatism, as demonstrated by the Rockefeller Institute workers in New York, there is a leukocytosis with a polynucleosis. The temperature is only moderately elevated in Schoenlein's disease, while in polyarticular rheumatism it is high. The pain in the joints in Schoenlein's disease is never as severe as in acute articular rheumatism.

HENOCH'S PURPURA

Henoch's purpura is a more severe affection than Schoenlein's purpura. This disease frequently affects the mucous membrane of the internal organs, especially of the gastro-intestinal tract. The symptoms may begin with severe gastro-intestinal pain preceding the appearance of cutaneous hemorrhages. Sometimes the gastro-intestinal symptoms alone may be present, simulating either appendicitis or some other gastro-intestinal disease. This makes the differential diagnosis difficult. The gastro-intestinal symptoms are due to hemorrhagic exudation into the intestinal wall. If this exudate affects the appendix, it causes marked distention of the organ with accompanying symptoms, and even at operation the distended appendix simulates an acute suppurative appendix. If an exudation into the intestinal wall occurs, especially one into the colon, bloody diarrheal stools or rectal tenesmus are present. The hemorrhages sometimes occur into the kidney, causing hemorrhagic nephritis and, in severe cases, anuria and retention of nitrogenous products in the blood. Occasionally the hemorrhage into the kidney may cause clotting of blood in the ureter, with symptoms of renal colic simulating renal calculus. Hemorrhages into the brain may occur, causing edema of the brain and convulsions. Hemorrhagic effusions into the joints are rare. Henoch's purpura may be familial and is subject to recurrence. The thrombocytes are diminished only in proportion to the anemia. The bleeding and coagulation time are not interfered with in either of these diseases.

Christian and others class the Schoenlein and Henoch's purpura with the various forms of erythema accompanied by abdominal symptoms first described by Osler³⁰. While it is true that these erythemas are frequently associated with abdominal symptoms, actual purpura and hemorrhages from the mucous membranes or intestines or other organs are usually absent in the erythema type of cases.

The etiology of the Schoenlein and Henoch's purpura is not definitely known though there is no doubt that anaphylaxis plays a rôle.

Purpuric hemorrhages under the skin, and even under the mucous membrane, may be secondary to any disease of the hematopoietic system, but in most instances they are seen together with leukemias and spleno-

megalic anemias In the lymphatic type of leukemia the hemorrhages occur chiefly from the gums, the mucous membrane of the mouth, the pharynx and, less frequently, from the nose In splenomegalic anemia especially in the so-called Banti symptom complex, hemorrhages set in late in the disease, and most frequently from the gastro-intestinal tract, especially the stomach In Gaucher's disease, hemorrhages are not common, but when they are observed they usually occur late in the disease In these cases neither the coagulation nor the bleeding time is interfered with The number of blood platelets is reduced, but is never out of proportion to the degree of anemia In splenomegalic hemorrhages the spleen aids in the destruction of the thrombocytes because in these cases the sinuses of the removed spleen show large numbers of destroyed thrombocytes Purpura may be secondary to severe infections, such as streptococcic and staphylococcic bacteremia, scarlet fever, measles, smallpox or typhus exanthematicus It may be found in the aged and weak It may occur in the terminal stages of secondary contracted kidney Cutaneous hemorrhages are seen in the course of affections of the liver without icterus but they are more frequent when icterus accompanies the liver disease

ENDOTHELIOSIS HEMORRHAGICA (MORBUS LITTEN)

Endotheliosis hemorrhagica was first observed by Litten in association with bacterial endocarditis (Libman) It is characterized by the presence of macrophages in the blood which possess a phagocytic property In addition to this, there is a decrease in the number of neutrophils and a relative increase in lymphocytes It seems that in this affection the defense against the streptococcus viridans is characterized by the absence of a myelocytic element which normally causes an increase in the neutrophilic leukocytes As the studies of Kuczinski and Wolf show, the defense is the work of the endothelial elements of the endothelium, the spleen and the kidney These findings are confirmed by Libman, Rosenthal and many others Libman is inclined to ascribe great importance to the macrophages in the process of immunity In bacterial endocarditis the petechiae are characteristic of hemorrhagic diathesis, hemorrhages from the mucous membrane of internal organs are absent The capillary stasis test usually is positive, but bleeding and coagulation time are normal and the number of thrombocytes is moderately reduced

TREATMENT OF ESSENTIAL THROMBOPENIA

As the specific cause is unknown, it is evident that the treatment must be symptomatic Blood transfusion of either direct or citrated blood has been advocated The beneficial effect of blood transfusions in this

disease is not as startling as the results following hemorrhages, or as is sometimes the case in pernicious anemia or anemia due to leukemia. It should be tried, but should not be repeated if the hemorrhages are aggravated as sometimes happens. Cacodylate of soda, from 1 to 3 grain (0.06 to 0.19 gm.) doses intramuscularly every day may be employed. For the symptoms of collapse hypodermoclysis with 250 c.c. of Ringer's solution is of great value. The calcium contained in the Ringer's solution also has a beneficial hemostatic effect. In the protracted and recurrent type of cases, the removal of the spleen as proposed by Kaznelson should be resorted to. The thrombocytes usually increase in number soon after the operation.

In a case reported by Charlotte Ehrenberg the blood platelets, which were 10,000 before the operation, rose to 87,000 two and a half hours after the operation, and the bleeding stopped at once. In some cases a few days after the operation the thrombocytes may rise as high as 500,000, which is more than normal. There is a case on record in which the blood platelets increased to 1,500,000 after the operation. After the initial increase the blood platelets again began to decrease in number, coming down as low as 50,000 or less. In spite of this the bleeding does not recur, although some of the phenomenon, like the Rumpell-Leede, may be present again. The removal of the spleen is not as a rule difficult and does not cause severe operative or postoperative bleeding. In a number of cases, however, suppuration in the left subdiaphragmatic space occurs after operation, and in many cases left sided pneumonia occurs. In the severe aplastic type of anemia the removal of the spleen is useless. Another treatment to be resorted to is the roentgen-ray treatment of the bone marrow and spleen and, sometimes, during the critical period, epinephrin injections and foreign protein may be used. Severe bleeding is also sometimes controlled by the intravenous use of from 10 to 30 c.c. of 10 per cent sodium chlorid solution or 20 c.c. of 10 per cent calcium chlorid solution, the latter should be given with great care directly into the vein, avoiding tissue infiltration because necrosis results if a drop of calcium chlorid solution escapes into the tissues. To avoid the necrosis that may follow calcium chlorid injection when leakage occurs into the tissue, Seelig³¹ advises the use of a 1 per cent calcium solution, the total amount being the same.

Treatment of Schoenlein and Henoch's purpura is chiefly symptomatic. Schoenlein's type usually runs a mild course and recovery ensues without any treatment. If the pains in the joints are troublesome, wet dressings and codein combined with calcium lactate internally

31 Seelig, M. G. Localized Gangrene Following the Hypodermic Administration of Calcium Chlorid, *J. A. M. A.* **84** 1413 (May 9) 1925.

are beneficial In Henoch's purpura, some authors advise large doses of animal charcoal, from 20 to 30 gm daily, for several days In the severe cases, intravenous injections of from 0.5 to 1 liter of Ringer's solution are beneficial The calcium contained in them is supposed to influence the capillaries favorably Calcium lactate in one-half table-spoonful doses is likewise advised ³²

32 It may be of clinical interest to record a personal communication from Dr. A. L. Amsterdam describing a patient who developed purpuric spots each time she took phenolphthalein

THE VALUE OF A STARCH-IODIN REACTION AS A TEST OF PANCREATIC FUNCTION *

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PHILADELPHIA

In 1924 Bassler devised a test for determining pancreatic function. With a view to establishing the practicability of this test and its adaptability for clinical purposes, this work was begun. We soon observed such marked variations in the results obtained by varying one of the reagents that we were led to undertake a detailed investigation of the test itself and of the various factors entering into it.

The Bassler test is presumably a test for pancreatic amylase and is designed to determine quantitatively that enzyme alone. In order to be of value as an index of pancreatic function this test presupposes the nondissociation of pancreatic enzymes, that is, if one enzyme is decreased the others are assumed to be proportionately diminished. This point is still far from settled. Against this nondissociation view may be cited the conclusions of Pawlow,¹ that the kind of food eaten calls forth an increase in the secretion of the enzyme specific for that particular type of food. The work of Einhorn,² the application of his method in the study of normal subjects by Friedenwald and Sindler,³ the recent study by two of us⁴ on cholecystitis, as well as the complicated but probably more accurate methods (with regard to the basic principles of the chemistry of enzyme action) of McClure, Jones, Wetmore and Reynolds⁵ all tend to refute this view. The latter observers found, like Pawlow, that there was a relationship between the kind of food ingested and the enzyme concentrations of duodenal contents. They also found that in a study of a group of cases that gave readings between normal and subnormal a dissociation of the concentration of the various types

* From the gastro-intestinal clinic of the hospital of the Graduate School of Medicine of the University of Pennsylvania.

1 Pawlow, I. P. *The Work of the Digestive Glands*, London.

2 Einhorn, Max. *The Duodenal Tube*, Philadelphia, W. B. Saunders Company, 1921.

3 Friedenwald, J., and Sindler, J. *Fractional Analysis of the Duodenal Contents in Normal Individuals*, J. A. M. A. **177** 1469 (Nov. 5) 1921.

4 Piersol, G. M., and Bockus, H. L. *Pancreatic Enzymes in Cholecystitis*, Arch. Int. Med. **35** 204 (Feb.) 1925.

5 McClure, C. W., Jones, C. M., Wetmore, A. S., and Reynolds, L. *Studies in Pancreatic Function, Enzymic Concentrations of Duodenal Contents in Health and Disease*, Am. J. M. Sc. **167** 649-664 (May) 1924.

of enzymes occurred. This dissociation was characterized by a normal concentration of one or two enzymes while the remaining ones were much diminished below the minimum normal. Meyner⁶ also found that he was unable to recognize any definite relationship among the individual enzymes, and Spencer⁷ felt convinced that he could demonstrate a greater stimulation of a specific enzyme by a specific food.

The work of other investigators, on the other hand, tends to substantiate Bassler's view as to the nondissociation of pancreatic enzymes. Grote⁸ states that the general variation of the three ferments is uniform in their relationship. Wohlgemuth,⁹ in repeating Pawlow's experiments on pancreatic juice obtained through a traumatic pancreatic fistula in a man, was not able to demonstrate any relationship between the type of foodstuff fed and the degree of activity of the enzyme specific for that kind of food.

The technic of the Bassler test as we employed it was as follows. A duodenal tube was passed into the duodenum on an empty stomach, preferably in the morning. When the tip of the tube was ascertained to be in the duodenum, we used the method described by Lyon,¹⁰ 100 c c of 5 per cent Witte peptone solution was injected through the tube as an activator to the pancreas. The tube was clamped off for five minutes, then the duodenal contents were aspirated. The first fraction aspirated was used for the test, because Bassler¹¹ states that this contains the largest portion of pancreatic juice and represents the sudden liberation of the stored up secretion of the pancreas.

The following reagents were employed:

Solution A, prepared as follows. In a beaker 2 gm of corn-starch (Duryea) were placed, to this were added 100 c c of cold distilled water. This was mixed thoroughly and then heated. Under constant stirring the mixture was brought to boiling and then cooled.¹²

Solution B, a 1 per cent sodium chlorid solution. The standard buffer solution mentioned in the original description of the test was omitted as it is now regarded as nonessential.

6 Meyner, E. Study on Pancreatic Function, *Med Klin* **16** 678 (June 27) 1920.

7 Spencer, G. F. *J Lab & Clin Med* **9** 261-267 (July) 1920, *ibid* **9** 261 (Jan) 1924.

8 Grote, L. R. Diagnosis of Pancreas Function from Duodenal Contents, *Zentralbl f inn Med* **43** 777-792 (Dec) 1922.

9 Wohlgemuth, J. *Berl klin Wchnschr* **44** 47, 1907.

10 Lyon, B. B. V. Nonsurgical Drainage of the Gallbladder, Lea & Febiger, 1923, p. 313.

11 Bassler, A. A Quantitative Test of Digestive Pancreatic Activity Easily Applied Clinically, *Arch Int Med* **35** 162 (Feb) 1925.

12 Ferris, H. C., Smith, E. E., and Graves, E. V. *J Am Dent A*, January, 1923.

The standard Bassler reagent was then prepared by combining solutions A and B, as follows To Solution A, when cool, 25 c c of Solution B was added and enough distilled water to bring the volume of the mixture up to exactly 400 c c This standard reagent was freshly prepared each day

In addition to these solutions, at first a tenth normal iodine solution, kept in a bottle with a dropper cork, was prepared After the first series of tests, this solution was changed to a twenty-fifth normal iodine solution, a strength which has been found more satisfactory and to which we have adhered in all our subsequent work

The actual procedure employed in carrying out the complete test is a modification of the method devised by Smith¹² in testing for ptyalin

Ten tubes of equal size were placed in a rack and numbered from 10 to 1 Into each of the ten tubes there was accurately pipetted, with a 1 c c pipet graduated in hundredths, definite quantities of duodenal return, water and the standard reagent The quantities in cubic centi-

TABLE 1—Quantities of Duodenal Return, Water and Standard Reagent

	Duodenal Return, C c	Water, C c	Bassler's Reagent, C c	Result in Bassler Units, per 100 C c
Tube 10	0.1	0.9	4	20
Tube 9	0.11	0.89	4	18
Tube 8	0.125	0.875	4	16
Tube 7	0.14	0.86	4	14
Tube 6	0.17	0.83	4	12
Tube 5	0.2	0.80	4	10
Tube 4	0.25	0.75	4	8
Tube 3	0.33	0.67	4	6
Tube 2	0.5	0.5	4	2
Tube 1	1.0	0.0	4	2

meters of these materials that are added to each tube are shown in Table 1

When prepared and shaken, the rack was put in an incubator at 38 C for forty minutes The rack of tubes was then taken out, the contents of each tube was shaken, and one drop of tenth normal solution of iodine was added to each tube Twenty minutes later the estimation of the amount of pancreatic amylase in terms of Bassler units was made according to readings obtained from the furthest tube to the left that was achromic When there was no achromic tube, but instead one side of the rack was pink and the other side green, the reading was taken between the adjacent pink and green tubes The result in Bassler units was obtained by multiplying the number of the achromic tube by 2 The details of these calculations may be found in Bassler's original article¹¹ The normal reading is supposed to lie between 8 and 14 units, the unit being defined as the quantity of amylase that will digest 1 gm of starch under the conditions outlined

In the first series of cases on which we tried the test as described above, we were struck by the consistently low readings obtained. These low readings occurred in spite of the fact that in the series there were several patients in whom there was no reason to suspect any pancreatic deficiency (Table 2, Series A). In this series there were fourteen cases, of which only two gave readings of 4 units each, the highest reading obtained in this group.

In accordance with a subsequent correction in the technic offered by the originator of this method, the iodine used for indicator was changed from tenth normal to twenty-fifth normal. The test was then repeated with this modification, the other reagents being unchanged. This group consisted of twelve cases, some of which had been used in the first series (Table 2, Series B). We now found that the results obtained

TABLE 2—*Variabilities of the Reaction with Different Amounts of Iodine Solution*

Series A			Series B		
Case	Pancreas at Operation	Results in Bassler Units with Tenth Normal Iodine, 3 Drops	Results in Bassler Units with Twenty-fifth Normal Iodine, 1 Drop	Pancreas at Operation	Case
1	Normal	2	20	Normal	1
2		3	20		2
3		3	20		3
4	Shotlike areas in head	4	20	Normal	15
5		3	20		16
6		3	20		17
7		4	20	Slight hardening of head	18
8		2	20	Normal	19
9		0	14		20
10	Chronic interstitial pancreatitis, biopsy	0	14		21
11		2	20		22
12		3	20		23
13		0			
14		3			

were all consistently too high. There were nine cases with readings of 20 units each, and the lowest obtained in the series was a reading of 14 units.

In doing the test we had noted what a marked variation in the reaction could be produced by varying the amount of iodine added. This led us to seek an explanation of this phenomenon, which appeared a serious objection to the test. Dr. Wilson, professor of physiologic chemistry in the University of Pennsylvania, on being consulted, suggested the possibility that some of the substances entering into the reaction might have the power of taking up iodine. He looked on the peptone or unsaturated fatty acids in the bile or duodenal juice as substances likely to possess such power. On his suggestion, therefore, we undertook an investigation of each substance entering into the reaction with a view to determining their iodine absorption power.

IODIN ABSORPTION BY PEPTONE

Four series of ten tubes each were taken. Peptone solution of varying strength was used in each series, namely, 0.25 per cent, 0.5 per cent, 1 per cent and 2 per cent. The strength and quantities of the other reagents were the same as used in the Bassler test. To each tube there was then added 1 drop of twenty-fifth normal iodine solution and the tubes were then allowed to stand at room temperature for twenty minutes. At the end of this time, 4 c.c. of Bassler starch solution was added to each tube with the following results:

0.25 Per Cent Series. Tubes 1 and 2, very slight starch iodine reaction, Tubes 3 to 10, inclusive, gave a definite starch iodine reaction.

0.5 Per Cent Series. Tubes 1, 2 and 3, achromic, Tubes 4 to 10, inclusive, definite starch reaction.

1.0 Per Cent Series. Tubes 1 to 5, inclusive, achromic, Tubes 6 and 7, very slight starch iodine reaction, Tubes 8, 9 and 10, definite starch iodine reaction.

2.0 Per Cent Series. All tubes achromic.

These observations suggested that the amount of iodine absorbed varied directly with the strength of the peptone solution present.

IODIN ABSORPTION BY DUODENAL FLUID

Duodenal tubes were passed on three fasting patients. When the tip was ascertained to be in the duodenum, the tube was connected to a drainage bottle and the duodenal residues collected by siphonage.

Three sets of ten tubes each were taken. To one set, 0.5 c.c. quantities of duodenal residuum from Patient 1 were placed in each tube. The second set contained like amounts of duodenal residuum from Patient 2, and in the tubes of the third set 0.5 c.c. of duodenal residuum from Patient 3 was placed. Twenty-fifth normal iodine solution was then added to the tubes of each series, starting with 1 drop in Tube 1, and increasing the amount added to each successive tube by 1 drop, until 10 drops were added to Tube 10. The tubes were then shaken and allowed to stand at room temperature for twenty minutes. At the end of this time 4 c.c. of Bassler starch solution was added to each tube. The results were as follows:

Patient 1. Tubes 1, 2 and 3, achromic, Tube 4, slight starch iodine reaction, Tubes 5 to 10, inclusive, definite starch iodine reaction.

Patient 2. Tubes 1 to 5, inclusive, achromic, Tubes 6 to 10, inclusive, definite starch iodine reaction.

Patient 3. Tubes 1 to 9, inclusive, achromic, Tube 10, definite starch iodine reaction.

Thus it appears that the duodenal fluid itself introduces a second important variable with regard to iodine absorption. Incubation of the juice before adding the iodine had no effect on this absorption power. The duodenal fluid was also found capable of splitting the starch-iodine combination, with the removal of the color from a starch-iodine solution. Similar reactions were carried out with duodenal contents after stimu-

lation with peptone It was found that this fluid took up more iodine than either the peptone solution or the fasting duodenal juice alone

This is shown by comparing the figures in Table 3 The first two columns represent readings obtained by carrying out the Bassler test on fasting duodenal residuum It will be noted that a marked difference in the readings is brought about by increasing the addition of iodine by

TABLE 3—*Variations in Results, Expressed in Bassler Units, of Regular Bassler Test when Carried Out with Varying Quantities of Iodine on Duodenal Residuum Before and After Stimulation with Peptone Solution*

Case	Fasting Duodenal Residuum		Duodenal Residuum After Peptone	
	Twenty-Fifth Normal Iodine, 1 Drop	Twenty Fifth Normal Iodine, 2 Drops	Twenty-Fifth Normal Iodine, 1 Drop	Twenty Fifth Normal Iodine 2 Drops
1	8	2	20	14
2	4	2	20	14
3	12	2	20	18
4	6	2	20	20
5	5	4	20	20
6	20	6	20	20

TABLE 4—*Two Types of Technic*

Technic of Bassler Test	Modified Technic
1 Pass duodenal tube	1 Pass duodenal tube
2 Stimulate pancreas with 5 per cent Witte peptone solution	2 Stimulate pancreas with 5 per cent Witte peptone solution
3 Aspirate duodenal contents after 5 minutes	3 Aspirate duodenal contents after 5 minutes
4 Prepare 10 tubes as for test	4 Prepare 10 tubes as for test
5 Incubate	5 Incubate
6 Add 1 drop of twenty fifth normal iodine to each tube	6 Determine iodine absorption factor <ol style="list-style-type: none"> Use 10 tubes with 0.5 cc of duodenal return in each tube Put 0.05 cc of twenty fifth normal iodine in Tube 1, increasing by 0.05 cc in each succeeding tube to 0.5 cc in Tube 10 Shake, stand at room temperature 30 minutes Add 4 cc of Bassler starch solution to each tube Read achromic tube containing largest amount of iodine Calculate amount of iodine absorption for each tube in test Add calculated amount of twenty fifth normal iodine to each tube plus 0.05 cc in excess
7 Read in 20 minutes	7 Read in 20 minutes

a single drop In the other two columns, which represent the results of the Bassler test done on duodenal residuum after peptone stimulation, the change occasioned by an additional drop of iodine is very slight The explanation of these variations lies in the fact that in fasting duodenal residuum, we have only one substance or group of substances which is capable of taking up iodine, while in the peptone stimulated duodenal residuum an additional substance capable of iodine absorption also is

present. In other words, the addition of a second drop of iodine to the duodenal residuum alone furnishes enough excess iodine to bring out a starch-iodine reaction in several additional tubes, whereas in the tubes containing both the peptone and the duodenal juice, there was present another substance capable of taking up the additional iodine so rapidly that no change or only a slight change in the readings occurred.

The foregoing observations furnish an explanation for the wide variation in the results obtained by varying the quantity of iodine employed in the test. In other words, there are substances present in this test which are capable of taking up such large quantities of iodine, as compared to the amount used in the test as originally proposed, that it is unnecessary to have any starch digestant present in order to obtain achromic tubes. Hence, readings suggestive of the presence of amylase may be obtained even if there is no pancreatic juice at all in the material tested.

In order to overcome this apparently serious objection to the test and to increase its reliability by accounting for the important variables that were obviously present, it seemed necessary to determine the iodine absorptive power of the duodenal return after peptone stimulation and to account for it in some way in the final step of the reaction. This was accomplished as follows. All the steps in technic as originally described were carried out until the final one. At this point a method was devised for determining what may be called the iodine absorption factor for the duodenal return.

A series of ten tubes numbered from 1 to 10 were taken. In each tube was placed 0.5 c.c. of duodenal return. To Tube 1 there was added 1 drop of twenty-fifth normal iodine solution. The addition of iodine solution to each succeeding tube was increased by 1 drop, thus, 10 drops were added to Tube 10. The contents of each tube were mixed thoroughly and allowed to stand at room temperature for thirty minutes. This provided adequate time for saturation of the duodenal return with iodine. To each tube 4 c.c. of Bassler starch solution was then added and the tube with the largest amount of iodine which failed to show any starch iodine reaction was then determined. The number of this tube was multiplied by 2. The result showed the number of drops of twenty-fifth normal iodine which 1 c.c. of that particular duodenal return was capable of absorbing. From this figure the iodine absorptive power of the quantity of duodenal return in each tube of the Bassler test was calculated, e.g., for Tube 10, one tenth of the amount, for Tube 9, eleven-hundredths, and so on. The final step in the test, when the iodine was to be added, being reached, the calculated amount of iodine necessary to take care of the iodine absorption factor as previously determined plus one drop in excess of this amount was added to each tube. The

determined amount was to allow for the absorption by the duodenal return, and the additional drop to react with any starch or products of starch digestion which still remained

It soon became apparent that if the iodin was to be added accurately quantitatively, the drop method was not sufficiently exact. Therefore, we changed to the pipet for determining the iodine absorption factor. An accurately calibrated pipet was employed and for each drop used in the method outlined, 0.05 c.c. was substituted.

Table 4 shows a comparison between the original Bassler test and the same test as modified by the estimation of the iodine absorption factor.

Table 5 shows the difference in the results obtained on the same patient when the regular Bassler test was employed and when the test was modified by determining and allowing for the iodine absorption factor. In the latter modification it will be noted that even after repeated estimations the results are encouragingly uniform.

TABLE 5—Comparison of Bassler Test with Its Modification

Case	Modified Technique												
	Regular Bassler Test Results in Bassler Units	Iodin Absorption Factor, C c		Iodin Absorption Factor, C c		Iodin Absorption Factor, C c		Iodin Absorption Factor, C c		Iodin Absorption Factor, C c		Iodin Absorption Factor, C c	
	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units	Bass-ler Units
1	20	4	0.3	5	0.5	4	0.3	4	0.5	3	0.4	3	0.4
2	10	0	0.5	0	1.0	0	0.3	0	0.4				
3	12	4	1.0	3	0.6								
4	20	20	0.9	18	0.7	18	0.7	18	0.8				
5	12	3	0.6	5	0.4								
6	20	3	0.3	4	0.3	4	0.2						
7	20	10	0.5	10	0.3	7	0.5	8	0.5				
8	20	6	0.5	5	0.4	7	0.4						
9	18	4	0.6	3	0.5	3	0.5						

It would seem that in this test for pancreatic function as originally devised, important variables have been overlooked. It is believed that at least the most serious ones have been pointed out and that a means has been suggested for overcoming them. This modification is offered with a certain amount of reservation, not because of the method itself but because of the factors entering into the reaction. While it is true that with these modifications it has been possible to obtain consistent results from day to day on the same patient even though the iodine absorption factor varied greatly, doubt as to the reliability of any starch-iodine reaction must still exist, because such a reaction must at best be an uncertain and changeable one in the presence of body fluids.

The bile from two gallbladders of cows obtained from freshly killed animals gave readings of 8 and 9 units by the Bassler technique, but failed to show any evidence of amylolytic activity by the modified technique when the iodine absorption factor was taken into consideration.

Aside from any question as to the value of the reaction itself, a far more important question remains to be settled, namely, whether or not testing duodenal juice for an amylolytic ferment is actually a test for pancreatic amylase. There is some doubt as to whether this amylolytic ferment, when found, has had its only source in the pancreas. Grutzner,¹³ Mendeldorp¹⁴ and Glaessner¹⁵ have all conclusively demonstrated the presence of a diastatic ferment in the extract of duodenal gland substance of various animals. Pawlow¹ states that the juice secreted by the duodenal glands unquestionably contains a diastatic enzyme. Beigman, Dukes and Yarborough¹⁶ found that of sixty-five intestinal extracts from five species of animals (ox, horse, pig, sheep and dog) only three failed to digest starch in neutral solution. Even extracts of submucosa of ileum and colon showed greater power of splitting starch than extracts of other regions of the intestines. They also were able to obtain powerful amylolytic action from extracts of skeletal muscle, mesenteric lymph glands, epidermic and dermal, and subcutaneous tissue in the pig. The apparently universal distribution of this amylolytic ferment makes the value of a test for pancreatic function based on this enzyme alone highly problematic.

The argument may be advanced that conclusions applied to man from experiments done on lower animals are unjustifiable. However, in one instance at least, it was possible to obtain a portion of duodenum from a patient examined at necropsy immediately after death. A glycerin extract of mucosa and one of submucosa was prepared by Dr. Fred Boerner who used the method described by Bergman, Dukes and Yarborough¹⁶. These extracts were tested for the presence of an amylolytic ferment. The method of Bassler was used, but instead of determining undigested starch by adding iodine at the end, each tube was tested for the presence of sugar. Definite reducing reactions with Benedict's solution were obtained and the tubes containing the largest amounts of extract gave the strongest reactions.

13 Grutzner, P. *Arch f diges Physiol* **12** 265, 1876

14 Mendeldorp, cited by Luciana. *Human Physiology*, trans by Welby, London, 1913, **2** 124

15 Glaessner, Karl. *Beitr z chem Phys u Path* **1** 105, 1901-1902

16 Bergman, H. D., Dukes, H., and Yarborough, J. H. *A Study of the Enzymic Action of Extract of the Duodenal Gland Regions of Domestic Animals*, *J Am Vet M A* **18** 313 (June) 1924

SOME METABOLIC ASPECTS OF CALCIUM THERAPY*

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It was shown by Marriott and Howland¹ that retention of phosphoric acid was an important factor in the acidosis which develops in nephritis. It was also pointed out by the same authors that although the acidosis could be overcome by administration of alkali, such as sodium bicarbonate, little else was accomplished. There was no reduction of serum phosphate. They also suggested the possibility of calcium therapy as a means of eliminating phosphates by the bowel.

More recent work on calcium therapy has been especially concerned with the problem of edema in nephrosis, and it appears² that calcium chlorid or other salts, such as ammonium chlorid, which leave a residue of mineral acid, will, by bringing the hydrogen ion concentration of the tissues nearer to their iso-electric points, cause the elimination of sodium and edematous fluid. However, the questions of phosphate elimination and other effects of calcium on mineral metabolism have not been so extensively investigated.

This paper deals, first, with the effect of various alkalis and also of calcium chlorid on phosphate elimination in urine and feces, and, second, with the effect of calcium acetate on mineral metabolism.

PROTOCOLS

EXPERIMENT 1—*Effect of alkalis and of calcium chlorid on elimination of phosphorus in urine and feces*

F M, an instructor in the department of medicine, incidentally having a typical case of nephrosis with edema, restricted his diet on twelve consecutive days to measured amounts of prepared foodstuffs. During the fifth and sixth days he took in addition, in divided doses, a total of 60 cc of a 25 per cent calcium acetate solution, during the seventh and eighth days he took similarly 60 cc of a 25 per cent magnesium acetate solution, during the ninth and tenth days, 60 cc of a 25 per cent potassium acetate solution, and during the last two days, 60 cc of a 25 per cent calcium chlorid solution. Twenty-four hour specimens of urine and feces were collected for each of the last ten days of the experiment. The daily urines were terminated with the passing of the morning urine on arising, a single bowel evacuation occurred each day about an hour later. Total phosphorus was determined on each of the daily specimens, but the results (Table 1) are grouped into five periods of two days each.³

*From the department of medicine, St. Louis University School of Medicine.

1 Marriott, W M, and Howland, J. Phosphate Retention, Arch Int Med 18 708 (Nov) 1916.

2 Keith, N M, Barrier, C W, and Wheelan, M. Treatment of Nephritis and Edema with Calcium, J A M A 83 666 (Aug 30) 1924.

3 In both experiments excreta on the first two days were discarded as preliminary.

EXPERIMENT 2—*Effect of calcium on mineral metabolism*

A measured diet of known inorganic composition was taken by the subject (A P B) on ten consecutive days. On each of the last four days a measured amount of calcium acetate solution was taken by mouth. Urines and feces were collected to represent the twenty-four hour periods and determinations made on each of the various inorganic elements. Results of these are given in Table 2.

The diet consisted of

25 Gm	of peanut butter
25 Gm	of condensed milk (sweetened)
20 Gm	of deviled ham
140 Gm	of bananas
147 Gm	of graham crackers
20 Gm	of jelly
5 Gm	of prepared coffee (George Washington)
20 Gm	of sucrose
2,000 Gm	of tap water

The food value of this diet is approximately protein, 28 Gm, fat, 36 Gm, and carbohydrate, 204 Gm, with a heat value of about 1,250 calories. Although less than maintenance, this diet satisfied the appetite during the first two days and was adhered to throughout the experiment. The inorganic composition of the diet as determined from analysis was chlorine, 0.950 Gm, sulphur, 0.3136 Gm, phosphorus, 0.450 Gm, sodium, 1.707 Gm, potassium, 0.772 Gm, calcium, 0.2937 Gm, and magnesium, 0.2626 Gm.

Collection of twenty-four hour urines was terminated with the morning urine passed on arising. In this experiment the urines were preserved with chloroform. The daily feces, as in the previous experiment, also consisted of a single specimen passed within a half hour after breakfast. This breakfast consisted only of four graham crackers, 20 Gm of jelly, and coffee with sugar but not milk, and contained a relatively small amount of the daily inorganic intake.

On the last four days calcium acetate was taken as follows: 10 cc of a 20 per cent solution a half hour before the noon meal, 10 cc again a half hour before the evening meal, and 5 cc at bedtime. The amount of calcium taken daily in this way was approximately 1.14 Gm.

METHODS OF ANALYSIS

Urines were measured, diluted with distilled water to 1,500 cc, and mixed. Feces were passed through a sieve and diluted to 500 cc and mixed. Measured or weighed samples of urine, feces and food were dried and charred in a platinum dish, the charred mass extracted with water, and the residue ignited. This ash was dissolved in dilute hydrochloric acid, added to the water extract, and the whole evaporated to a convenient volume, from which aliquots were taken for the determinations of sodium, potassium, calcium, magnesium and phosphorus. Chlorine and sulphur were determined on separate samples. Calcium, magnesium, potassium and phosphorus were determined essentially as reported in a previous paper,⁴ however, in this study the samples taken for analysis contained approximately ten times as much of the inorganic element concerned as in the previous work which was done on blood plasma. Sodium was determined by the volumetric method of Kramer.⁵

4 Briggs, A. P. J. Biol. Chem. **57** 351 (Sept.) 1923

5 Kramer, B., and Gittleman, I. J. Biol. Chem. **62** 353, 1924

Chlorin was done by the wet ash method of Van Slyke,⁶ and sulphur by the method of Benedict.⁷

It is commonly stated⁸ that alkali causes more phosphates to be eliminated in the feces and less in the urine. In their study on the mineral metabolism of infants Shohl and Sato⁹ found a slight change in that direction with the administration of sodium bicarbonate. The

TABLE 1—*Excretion of Phosphorus During Two-Day Periods on Various Salts (Milligrams Phosphorus)*

	Period				
	Control	Calcium Acetate Solution	Magnesium Acetate Solution	Potassium Acetate Solution	Calcium Chlorid Solution
Urine phosphorus	976	494	935	905	690
Feces phosphorus	623	510	585	625	650
Total	1,599	1,504	1,510	1,530	1,340

TABLE 2—*Minerals Excreted in Urine and Feces (Milligrams per Twenty-four Hours) in Experiment 2*

	Sodium	Potassium	Calcium	Magnesium	Chlorin	Phosphorus	Sulphur
Urine control period	2,990 1,900 1,900 1,600	870 1,120 1,220 1,420	241 189 147 126	149 168 152 156	1,320 1,020 1,020 790	484 484 455 470	520 400 394 206
Total	8,390	4,630	703	625	4,150	1,893	1,520
Urine calcium acetate period	1,700 2,300 1,400 1,300	1,120 1,280 1,280 1,280	315 294 284 294	196 173 156 180	945 826 826 915	395 234 250 220	437 350 330 384
Total	5,700	4,960	1,187	705	3,512	1,099	1,501
Feces control period	370 130 130 230	180 100 110 180	415 161 77 168	369 68 75 78	20 16 11 11	470 117 154 263	150 111 148 63
Total	860	570	821	690	58	1,004	472
Feces calcium acetate period	200 400 400 370	100 180 123 88	455 1,245 980 1,110	123 246 151 109	12 15 12 16	360 625 360 264	82 143 76 96
Total	1,370	491	3,790	629	55	1,609	397

results shown in Table 1 indicate that potassium or magnesium acetate have little influence on the partition of phosphorus, whereas either calcium acetate or calcium chlorid lead to the diversion of considerable amounts of phosphorus from the urine to the feces. This brings to mind the experiments of Fiske and Sokhey¹⁰ in which the administra-

6 Van Slyke, D. D. J. Biol. Chem. **58** 523 (Dec.) 1923

7 Benedict, S. R. J. Biol. Chem. **6** 363, 1909

8 Shohl, A. T. Physiological Rev. **3** 529 (Oct.) 1923

9 Shohl, A. T., and Sato, A. J. Biol. Chem. **58** 248 (Nov.) 1923

10 Fiske, C. H., and Sokhey, S. S. J. Biol. Chem. **63** 309 (March) 1925

tion of small amounts of mineral acid by various pathways led to no change in phosphate excretion

Values for the minerals excreted in the second experiment are given in Table 2. Balances for each are shown in Table 3. Since the diet in this experiment was below maintenance, the deficiency was probably met at the expense of skeletal muscle.¹¹ This probably accounts for the negative balances of potassium, magnesium, phosphorus and sulphur.

Sodium and chlorine were in approximate equilibrium during the greater part of the experiment.

TABLE 3—*Balance of the Various Minerals in Experiment 2*

	Sodium	Potassium	Calcium	Magnesium	Chlorin	Phosphorus	Sulphur
Control Period							
Urine	8,390	4,630	703	623	4,150	1,893	1,520
Feces	860	570	821	690	58	1,004	472
Total	9,250	5,200	524	1,314	4,208	2,897	1,992
Intake	6,828	3,038	1,175	1,040	3,790	1,800	1,254
Balance	-2,422	-2,112	-349	-274	-418	-1,097	-738
Calcium Acetate Period							
Urine	5,700	4,960	1,187	705	3,512	1,099	1,501
Feces	1,370	491	3,790	629	55	1,609	397
Total	7,070	5,451	4,977	1,334	3,567	2,708	1,898
Intake	6,828	3,038	5,715	1,040	3,790	1,800	1,254
Balance	-242	-2,363	+738	-294	+223	-908	-644

TABLE 4—*Daily Excretion of Ammonia in Experiment 2*

	Day							
	3	4	5	6	7*	8	9	10
Cubic centimeters of tenth normal ammonium hydroxid	190	173	173	173	121	104	104	86

* Calcium acetate was taken on the last four days

With the ingestion of calcium acetate, the small negative calcium balance was changed to a positive one. Presumably depleted calcium reserves were being restored at this time, and the coincident decrease in the negative phosphorus balance indicates the storage of some calcium phosphate.

In spite of a definite decrease in total phosphorus elimination during the calcium acetate period, there is a conspicuous increase in the phosphorus excreted with the feces. In a clinical report to follow it will be shown that the elevated plasma phosphate in nephritis can be brought down to normal by the administration of calcium acetate.

The excretion of sodium, potassium and magnesium is not appreciably influenced by calcium acetate, which, together with other recent

work,¹² supports the theory that the increased sodium elimination following the administration of calcium chlorid is due, not to an antagonism between cations, but to the residue of hydrochloric acid from excretion of calcium by the bowel

As previously stated, it seems probable that the positive balance for calcium with the administration of calcium acetate is due to the storage of calcium carbonate and phosphate in solid tissues. Certainly there appears to be nothing brought out in this study to suggest that administration of calcium acetate to a nephritic patient would lead to retention of alkali with edema.

Whether various other salts are excreted in the urine passively or not, the ammonia appears to be synthesized by the kidney¹³ as an important agent in neutrality regulation and base conservation,¹¹ hence the increase of ammonia found in the urine following the administration of calcium chlorid which leaves a residue of hydrochloric acid. On the other hand, the administration of an organic salt of calcium, such as calcium acetate, should tend to decrease the formation of ammonia, since the organic radicle would be oxidized and eliminated by the lungs and the calcium component would divert a part of the phosphoric acid from the urine to the feces. Ammonia was determined in the urines in Experiment 2. The results shown in Table 4 support the contention that a certain amount of the phosphoric acid load has been taken by the intestine from the kidney.

SUMMARY

Calcium acetate given by mouth causes the diversion of a considerable amount of the excreted phosphoric acid from the urine to the feces.

The relief from this phosphoric acid load necessitates the synthesis of a smaller amount of ammonia by the kidney.

The administration of calcium acetate affords a means of correcting the phosphoric acid retention in nephritis free from the disadvantages of alkali retention and resulting edema which is observed with sodium bicarbonate therapy.

12 Keith (Footnote 2) Atchley, D. W., Loeb, R. F., and Benedict, E. M. *Physicochemical Studies of Calcium Chlorid Diuresis*, J. A. M. A. **80** 1643 (June 2) 1923.

13 Nash, T. P., and Benedict, S. R. *J. Biol. Chem.* **48** 463 (Oct.) 1921.

EFFECTS OF INTRAVENOUS INJECTIONS OF ACRI- FLAVINE IN SEPSIS

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The last few years have witnessed the trial of several antiseptic dyes, intravenously, in sepsis and bacteremia. Of these, neutral acriflavine, gentian violet and meicrochrome have been reported favorably.

Acridine, of which the chemical formula is 3-6 diamino-10 methylacridinium dihydrochlorid, was introduced by Ehrlich, who found it effective against trypanosomes and who called it trypanflavine. Browning,¹ who had worked with Ehrlich, together with his co-workers, found that the dye was antiseptic, that it maintained its efficiency even in serum, and that a solution of 1:100,000 killed staphylococci and *Bacillus coli*. They also advocated the use of the dye in war wounds as a dressing after proper surgical measures had been taken. The dye was used intensively by a number of the British surgeons, but not all would subscribe to its value. Ligat² found it useful, but most³ of them emphasized the early use of débridement and the relative inertness of the dye in later stages of infected wounds. In arguments against Browning's data of the potency of acriflavine, Fleming⁴ administered the dye intravenously to a rabbit and then found the blood to have no effect on staphylococci. Hewlett⁵ also found the dye much weaker than Browning stated.

Because of its penetrating power the drug was used locally in the treatment of gonorrhea by a large number of observers with contradictory results.⁶ Finally, it was used intravenously for the treatment

* From the medical service of the Fifth Avenue Hospital.

1 Browning, C. H., Gulbranson, R., Kennaway, E. L., and Thornton, L. H. D. Flavine and Brilliant Green, *Brit. M. J.* **1**: 73 (Jan. 20) 1917.
Browning, C. H., Gulbranson, R., and Thornton, L. H. D. Antiseptic Properties of Acriflavine and Proflavine, *Brit. M. J.* **2**: 70 (July 21) 1917.

2 Ligat, D. Flavine and Brilliant Green in the Treatment of Infected Wounds, *Brit. M. J.* **1**: 78 (Jan. 20) 1917.

3 Drummond, H., Hamilton and McNee, J. W. Treatment of a Series of Recently Infected War Wounds with Flavine, *Lancet* **2**: 641 (Oct. 27) 1917.
Colledge, L., Drummond, H., Worthington, R. T., McNee, J. W., Sladden, A. F., and McCartney, J. E. Treatment of a Series of Recently Infected War Wounds with Proflavine, *Lancet* **2**: 676 (Nov. 3) 1917.

4 Fleming, A. Physiological and Antiseptic Action of Flavine, *Lancet* **2**: 340 (Sept. 1) 1917.

5 Hewlett, R. T. Germicidal Power of Flavine, *Lancet* **2**: 621, 1917.

6 Hyman, Abraham. Acriflavine in the Treatment of Gonorrhea, *Urol. & Cutan. Rev.* **24**: 325, 1920.

of puerperal and other infections Bohland⁷ reported its use in ten cases of influenza and pneumonia, in which he obtained great improvement with lysis. One other patient, however, developed meningism and empyema, despite the treatment, before recovery. He cites another case, one of pyelonephritis with cystitis with recovery, and also three cases of puerperal sepsis. Bohland used a solution of 0.5 per cent and gave 0.1 gm daily. He recommended the drug in all cases of sepsis.⁸ Cramer,⁹ in ten cases out of eleven of puerperal fever, got good results, but in one case of sepsis following tonsillar abscess, death followed. Whitehouse¹⁰ used a solution of 1:1,000 intravenously in doses of from 10 to 15 cc daily and was pleased with the results, but he reserved his judgment of its value. Spiess,¹¹ in a case of post-operative meningitis following transnasal removal of an hypophyseal tumor, revised and drained the operative site and gave trypaflavin intravenously, with recovery by the patient.

We have administered neutral acriflavine by the intravenous route, using the commercial preparation especially purified for that purpose, in eleven cases of generalized infection. Of these, six had a positive blood culture, and it is to these that we wish to call attention, since these cases, we consider, offer a direct criterion of the efficacy of the drug. In each case a 1 per cent solution was freshly prepared with physiologic sodium chlorid solution made that same day from freshly distilled water, then filtered and sterilized by boiling for twenty minutes. The average dose was 5 mg of the dye per kilogram of body weight, at intervals stated in the protocols. In general, the injections were well tolerated, the only untoward symptom being nausea and, rarely, vomiting in one or two of the patients. No hematuria or suppression or other evidence of damage in renal function was noted in these patients, such as found by Bohland⁷ in a nephritic patient or by Meleney and Zau¹² in experimental work on rabbits.

REPORT OF CASES

CASE 1—*Carbuncle of lip, lobar pneumonia, septicemia (Staphylococcus aureus)*. R. P., a man, aged 30, had an infection of the upper lip of twenty-four hours' duration, which had started from a small fever blister, and was accom-

7 Bohland, K. Intravenöse Anwendung des Trypaflavins bei Infektionskrankheiten, *Deutsch med Wchnschr* **45** 797, 1919.

8 Bohland, K. Trypaflavine, ein inneres Antisepticum, *Med Klin* **15**:1173, 1919.

9 Cramer. Erfahrungen mit intravenöser Injektion des Trypaflavins bei puerperalen Infektionen, *Deutsch med Wchnschr* **46** 311, 1920.

10 Whitehouse, H. B. Surgical Treatment of Puerperal Sepsis, *Brit M J* **2** 267 (Aug 21) 1920.

11 Spiess, G. Heilung eines Falles von Meningitis nach endonasaler Operation eines Hypophysentumors durch Trypaflavininfusionen, *Deutsch med Wchnschr* **46** 207 (Feb 19) 1920.

12 Meleney, F. L., and Zau, Z. Action of Acriflavine in the Blood and Certain Tissues of Rabbits, *J A M A* **84** 337 (Jan 31) 1925.

pained by chill, fever and abdominal rigidity. The patient was prostrated, showing marked swelling of the upper lip with pus oozing and signs of consolidation of the right lower lobe. The white cells totaled 12,000, of which the polymorphonuclears were 94 per cent and the lymphocytes 6 per cent. A blood culture showed *Staphylococcus aureus*, and a culture from the lip showed *Staphylococcus aureus*. The temperature ranged between 102.2 and 106 degrees.

Two injections of neutral acriflavine solution were given. The patient died two days after admission.

CASE 2—*Endocarditis acuta* A D, a woman, aged 44, with a history of measles, and of rheumatism at 17 and again at 41, was admitted complaining of fatigue and weakness for one month and shortness of breath for two weeks. She had a slight cough and occasional night sweats. The heart was found enlarged to the left, with a blowing murmur. There were moist râles over the posterior chest. The spleen was enlarged. The urine showed a faint trace of albumin, with occasional hyaline casts. Blood examination showed hemoglobin, 89 per cent, red cells, 4,000,000, white cells, 10,000, with 80 per cent polymorphonuclears. A blood culture showed *Streptococcus viridans*.

Beginning the third day in the hospital, acriflavine was given daily for eight doses. The temperature ranged between 102 and 97 degrees in a septic manner. Orthopnea and edema followed, with precordial distress. The patient died on the twelfth day in the hospital.

CASE 3—*Endocarditis acuta, Streptococcus viridans bacteremia* E R, a woman, aged 25, had a history of scarlet fever at 8, followed by rheumatism and heart trouble. At 14 she had rheumatism again and heart trouble. Sixteen days before admission she developed pains in the wrists, hands, chest and back. The pains involved all the joints for ten days, and stopped only to recur later together with vomiting. She was undernourished and irrational. Opisthotonos was present. The great toe phenomenon of Babinski was positive on the right and Kernig's sign was present. The urine had a heavy trace of albumin with red cells, pus and few casts. The heart was enlarged to the left, and a loud systolic blow was present over the precordium. A blood culture showed *Streptococcus viridans*, but the spinal fluid was sterile though bloody.

Neutral acriflavine was given intravenously every second day for five doses, then after a free period of ten days it was given daily for four doses. The temperature ranged between 97 and 106 degrees. Blood cultures remained positive. The hemoglobin, at first 81 per cent, fell to 47 per cent, the red cells from 3,800,000 to 2,500,000. The patient died three months after admission.

CASE 4—*Endocarditis subacuta Streptococcus viridans bacteremia* G M, a man, aged 23, had acute rheumatic fever at the age of 5 which kept him ill for two years and left him with impaired cardiac reserve. For three months before admission he had aches and pains of moderate severity, fever and a "cold" (possibly tonsillitis), and had to stay in bed. He was pale, the tonsils were large and red. The heart was enlarged, with a to-and-fro murmur at the apex and a diastolic murmur at the base. The liver and spleen were enlarged. The fingers were clubbed. Hemoglobin was 79 per cent, red cells totaled 4,000,000, white cells, 16,500, with polymorphonuclears 76 per cent and lymphocytes 24 per cent. The blood showed *Streptococcus viridans*.

The patient was given eleven injections of neutral acriflavine in a period of twelve days. These caused general discomfort, nausea and vomiting immediately afterward, and his skin, conjunctivae, urine and feces were all deep yellow. The blood culture, however, was persistently positive. He was given thirteen daily injections of sodium cacodylate, with no improvement. The hemoglobin gradually dropped to 53 per cent, the red cells to 2,700,000. He was twice transfused with whole blood by Dr S. A. Thompson. The patient died seven weeks after admission.

CASE 5—Typhoid fever D Z, a man, aged 24, was admitted complaining of malaise for five days and a chill four days before, followed by fever and sweats. The only positive physical findings were a congested pharynx and a

palpable spleen The white cells were 5,500, with polymorphonuclears 64 per cent, lymphocytes 26 per cent, transitionals 9 per cent and eosinophils 1 per cent The Widal agglutination test of the serum was negative for typhoid and paratyphoid, but the blood culture was positive for *Bacillus typhosus* The patient was only moderately sick

He was given five daily injections of neutral acriflavine, beginning three days after admission The temperature ranged between 102 and 104 degrees for twelve days, then gradually fell to normal No effects were seen from the acriflavine, and it was forty days after admission before negative stools were obtained and the patient relieved from quarantine

CASE 6—*Sepsis, Streptococcus hemolyticus, complicating diabetes* J A, a man, aged 48, had been under treatment for diabetes for more than a year He developed thrombophlebitis of one leg, with fever, prostration and coma A blood culture showed *Streptococcus hemolyticus*

He was given four injections of neutral acriflavine at intervals of eight hours There was no change and the patient died

Two of these cases were fulminating infections, one patient with *Streptococcus hemolyticus* dying within twenty-four hours from the time of initial observation and treatment, the other, with *Staphylococcus aureus*, dying in thirty-six hours from the onset One case of mild typhoid passed through the usual course even without apparent shortening of the period of infectivity Three cases of endocarditis with *Streptococcus viridans* bacteremia, with from nine to eleven injections of neutral acriflavine, ran their course unaltered, with no change observed in the positive blood culture at any time during or after the injection

In this connection it is of interest to review the work of Spencer¹³ He injected rabbits and fifteen minutes later tested the bactericidal effect of the blood on *Bacillus typhosus* in vitro, according to the looped pipet method of Wright A single injection of 1 c c of dye in a concentration of 1/100 caused no difference fifteen minutes afterward The test was repeated with *Staphylococcus aureus*, and repeated injections tried for cumulative effect Thus, after four injections at twenty minute intervals with the maximal tolerated dose, no change was found in the bactericidal power of the blood Similarly, on injecting white mice with the minimal lethal dose of pneumococcus culture followed by the maximal tolerated dose of acriflavine, none was saved Likewise, Meloney and Zau¹² found that when the dye was given intravenously to rabbits even in lethal doses, there were no bactericidal or bacteristatic properties for *Streptococcus hemolyticus* When a minimal lethal dose of washed hemolytic streptococcus (which would kill a control in from seven to ten days) was injected intravenously and treatment with acriflavine was instituted from twenty-four to forty-eight hours afterward, the dye did not prevent death but actually hastened it They found that with

¹³ Spencer, Harvey Effects of the Intravenous Injections of Acriflavine, J Lab & Clin Med 9 322 (Feb) 1924

lethal doses marked kidney damage was done and that with nonlethal doses there was a rise in blood urea during the first few days. They therefore concluded that there was no sterilizing action within the body of the rabbit and that the injury the dye produced in the liver and kidneys might even handicap the animal in its fight against the infection.

That many patients with severe infections who have received acriflavine have recovered is certainly undeniable. But on the other hand, in other cases of equal severity there has been recovery without such treatment. Spontaneous recovery in *Bacillus coli* sepsis was reported by Jacob¹⁴ in 60 per cent of thirty-nine cases. Coleman and Hastings¹⁵ reported three such cases, and recently Felty and Keefer¹⁶ have reported seventeen recoveries in a series of twenty-five cases (58 per cent). Likewise, spontaneous recovery occurs for other organisms. Thus, speaking of the serum treatment, Kolmer¹⁷ states "The tendency of acute streptococcus infections to end spontaneously by crisis must, however, be borne in mind, and the good results observed in individual cases may be coincident with, rather than the result of, the administration of serum."

We record two cases of *Streptococcus hemolyticus* sepsis in which there was recovery without any noteworthy treatment.

CASE 7—*Metritis, Streptococcus hemolyticus septicemia, recovery*. L. M., a girl, aged 18, a negress, was delivered normally of a healthy child two weeks before admission to the hospital. She was discharged well one week after delivery, and that night began to have severe, cramplike pain in the lower abdomen and in the side. The pains continued constantly for six days, but eased up on the morning of admission to the hospital. She had had complete anorexia, marked thirst and high fever. She was acutely ill, prostrate and very tender all over the abdomen, with rigid abdominal muscles. The uterus was enlarged almost to the umbilicus. The head and thorax were normal. The temperature was 103, the pulse, 120, and respiration, 36. The white cells totaled 22,400, with 73 per cent polymorphonuclears. A blood culture showed *Streptococcus hemolyticus*. The urine showed a trace of albumin, with occasional hyaline casts and white cells, both scattered and clumped.

The uterus was curetted forty-eight hours after admission and a small amount of secundines removed. Hot douches of a proprietary solution of an antiseptic preparation were given three times a day. The temperature varied between 103.8 and 98.4 for seven days, then stayed normal. Blood cultures eleven days after admission were sterile. The patient made a complete recovery.

CASE 8—*Streptococcus hemolyticus septicemia, secondary to otitis media and venous thrombosis, recovery*. J. H. K., a boy, aged 15, had had scarlet fever eight years before complicated by right otitis media. The following year the

14 Jacob, L. Colon Bacillus Septicemia, *Deutsch Arch f klin Med* **97** 303, 1909.

15 Coleman, W., and Hastings, T. W. Bacillus Coli Communis. The Cause of an Infection Clinically Identical with Typhoid Fever, *Am J M Sc* **137** 199, 1909.

16 Felty, A. R., and Keefer, C. S. Bacillus Coli Sepsis. Clinical Study of Twenty-Eight Cases of Blood Stream Infection by the Colon Bacillus, *J A M A* **82** 1430 (May 3) 1924.

17 Kolmer, J. A. Infection, Immunity and Biologic Therapy, Ed 3, Philadelphia, W. B. Saunders Company, 1924, p 893.

tonsils and adenoids were removed because of frequent sore throats and nose colds. He was well until one month before admission, when he developed bilateral earache, which kept him in the school infirmary for three days. Two weeks before admission he had frequent sensations of chill and a sore throat. Three days later the left ear ached, and five days later a myringotomy was done, with relief of only a few hours. Then he began to have a generalized headache which persisted although the left ear continued to drain pus for five days. He had sensations of chill and weakness afterward, and on the morning of admission he vomited. The temperature for the three days preceding ranged between 106 and 100.

The physical examination was entirely normal except for a slight serous discharge from the left ear. The eye-grounds were repeatedly examined and found normal. The white cells totaled 18,000, with 75 per cent polymorphonuclears. The temperature on admission was 100.4, then dropped to 98.6. A chill followed, and the temperature rose to 106. This dropped within twelve hours to 96, rose to 103, and gradually fell in the next two days to normal. A blood culture was positive for *Streptococcus hemolyticus* on admission, and again on the second and fourth days. One week after admission the blood culture was sterile. The boy made a complete recovery.

CONCLUSIONS

Of eleven patients with generalized infection who were treated with intravenous injections of neutral acriflavine, six had positive blood cultures. Of these six, five died despite the treatment. The sixth case, one of typhoid fever, ran the usual course and showed no shortening of the time necessary to procure negative stool cultures for release from quarantine.

We have seen no improvement following the intravenous use of neutral acriflavine in cases of sepsis or bacteremia.

There was spontaneous recovery in two cases of *Streptococcus hemolyticus* sepsis.

Book Reviews

MODERN MEDICINE, ITS THEORY AND PRACTICE IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS Edited by Sir William Osler Third edition, thoroughly revised, reedited by Thomas McCrae, assisted by Elmer H Funk Vol 1 Illustrated Philadelphia Lea and Febiger, 1925

The first volume of the third edition of Osler's Modern Medicine, revised and enlarged, contains many features which stamp it as a valuable "bread and butter" volume for the general practitioner. The aim of the editor has been to "keep an even balance between the condensation of a textbook and the elaborate treatment of the monograph." The volume contains Osler's original introduction of the first edition on the Evolution of Internal Medicine, an interesting chapter from an historical standpoint which contains much useful but not strictly medical information, it is valuable chiefly because it reflects Osler's point of view, as Osler himself lived through the period in which internal medicine as such evolved into a strict specialty.

Many of the original contributors have died. Sir William Osler, John H Musser, James Carroll, W P Dunbar, Isadore Dyer, John H McCollum, M Herzog, A O J Kelly, John McCrae, and E H Southard. In some instances their names have been retained at the head of the articles originally contributed by them but which have been revised, this is true of all of Osler's articles. This volume, on infectious diseases, contains chapters on the Introduction to the Study of Infectious Diseases, by Ludvig Hektoen, Typhoid Fever, by Thomas McCrae, Lobar Pneumonia, by George William Norris and David L Finley, Tuberculosis, by Edward R Baldwin, Diphtheria and Scarlet Fever, by John H McCollum and Edwin H Place, revised and brought up to date by Thomas McCrae and Elmer H Funk. This series promises to meet the requirements of the general practitioner, in providing an extremely helpful and usable reference work, and will undoubtedly meet with universal approval.

SYPHILIS UND INNERE MEDIZIN I TEIL, DIE ARTHRO-LUES TARDIVA UND IHRE THERAPIE By HERMANN SCHLESINGER Pp 165, 8 illustrations Price, 9 90 gold marks Vienna Julius Springer, 1925

This well written monograph concerning arthrosyphilis tarda is the first of a series devoted to syphilis and internal medicine. The two parts in preparation will deal with the relation of syphilis to other internal diseases and to the glands of internal secretion.

The present work, based on a study of thirty-five cases, describes the hitherto largely neglected forms of joint conditions due to syphilis in which other signs of syphilis are absent. The Wassermann reaction of the blood is of no value in diagnosis since it usually is negative and frequently remains negative throughout treatment. A positive reaction of the joint fluid, found in some cases, is of diagnostic significance. Luetin tests, also, are of no value. The writer believes that, exclusive of cases of septic origin, gonorrhea and late syphilis are the most frequent causes of the acute joint affections refractory to salicylates. Late syphilis is also responsible for a fairly large number of the varied group of chronic arthritides. The true nature of these cases is apt to be overlooked unless, particularly in every chronic joint affection aside from those of gouty, gonorrheal or traumatic origin, the possibility of syphilitic etiology is kept in mind.

The clinical classification offered includes arthralgias, acute or subacute febrile forms, chronic cases, atypical types and mixed forms. Tabetic arthrop-

athies are not considered as forms of arthrosyphilis. Spinal localizations are discussed under the headings of spondylitis syphilitica simplex and destructiva. The roentgen-ray findings are fully described. The criteria for diagnosis are tabulated and carefully evaluated and differential diagnosis considered. Pathologic anatomy receives attention. An extensive bibliography and an index are included.

This careful clinical study, directing attention to a group of joint conditions likely to be neglected as to diagnosis and treatment, is of practical importance and deserves wide reading. Its presentation is clear and concise.

TEXT BOOK OF PATHOLOGY Thirteenth Edition By F DELAFIELD and T M PRUDDEN Price, \$10 New York William Wood & Co

The thirteenth edition of Delafield and Prudden's well known Text Book of Pathology has appeared. On the whole, the form and arrangement of the contents have not been materially altered either in this edition or in recent former editions.

Attention is called in the preface to the large amount of chemical and physiologic data that is of interest in the field of pathology, much of which has not as yet been correlated or digested. To do this will take time. Authors of pathology textbooks and especially those concerned in the preparation of revisions will find a fertile field for many years to come in selecting and sifting contributions in both near and remote fields and arranging them in such a way that they will become satisfactorily incorporated in standard works. The tendency to multiply texts in various special or related fields will not solve the problem. The time allotted for courses in the medical curriculum is so limited that textbooks of wide scope but with condensed contents will always be necessary for medical students.

In this edition of Delafield and Prudden, the impression may be obtained that undue conservatism exists in the consideration of recent important contributions. For example, no mention is made of the work of Noguchi on yellow fever and the discovery of the *Leptospira icteroides*. So, too, though mention is made of the revision of the work on lung abscess and gangrene, the numerous contributions and the real advances that have been made in connection with the rôle of spirochetes in these processes are not set forth. It would seem, too, that a clearer statement than is given is now possible concerning the pathogenicity of the so-called influenza bacillus and its nonrelationship to epidemic influenza, in view of the numerous researches that have been completed since the last influenza pandemic.

On the whole, however, the more important contributions in the field have been reviewed or are mentioned in footnotes together with references that cover a wide range of literature. The book continues to be one of the most useful texts in its field and in many ways is better adapted for the teaching of pathology, as the subject has been developed in America, than any other.

THE MECHANISM OF CANCER METASTASIS*

MONTROSE T. BURROWS, M.D.

ST. LOUIS

In previous articles¹ it has been shown that cancer may be only the result of a primary crowding of cells and a relative reduction of the blood supply to the mass. The change leading to cancer is not a primary change in the cell but in the organization of the tissue. The cancer cell grows and has the morphology peculiar to it on account of its immediate environment. These changes that the cells suffer in the cancerous tissue are reversible. These cells in an environment similar to that of the normal organism revert to nongrowing differentiated cells. They continue to grow in the cancer because the cancerous organization is able to destroy the surrounding normal tissue and blood vessels and reproduce the conditions necessary for the continuation of their growth.

It has been asked if cancer is due to such conditions how may the cancer cells break loose from the main tumor mass, migrate to distant parts, grow and form new tumors or metastases. The conception of cancer, as outlined above, has been the outcome of studies of the independent growth of normal body cells in the tissue culture. These studies have shown absolutely that growth, differentiation and function as they are seen in cancer and the normal organism are not determined by the cells, but are each simple responses of these cells to their immediate environment. The changes, such as growth, differentiation and function, which each cell suffers in normal development, are not determined by itself but by other more general formative forces in the organism. The cancer cell is not different from the normal cell, but merely a normal cell reacting to the immediate conditions of stagnation of environment and cell crowding.

The idea now more generally held assumes that the cancer cell is different from the normal cell. It is a cell equipped with a special mechanism for migrating about in the organism and one which can

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¹ Burrows, M. T. South M. J. **17** 233 (April) 1924, four articles in Proc Soc Exper Biol & Med **21** 94, 1923, letter, J. A. M. A. **82** 323 (Jan 26) 1924. Radiology **4** 407 (May) 1925. Burrows, M. T., and Johnson, C. S. Action of Oils in Production of Tumors with Definition of Cause of Cancer, Arch Int Med **36** 294 (Sept) 1925.

grow independently under all conditions. This idea has not been built on careful analysis of the facts in the case, but is purely a theoretical notion built entirely on casual observations of the process.

The same idea of the independence of the cell has also permeated widely into a great deal of our modern biologic teaching. As Wilson² has clearly pointed out, however, many of the best biologists of the last and of the present century have been unable to find facts in support of this view. The picture of normal development of an animal or man is the action of some general formative force. The growth, differentiation and function of cells are secondary and wholly under its control.

As I have pointed out in previous articles there is no evidence that the cancer cell can grow independently in a tissue culture under other conditions than those necessary for an equally independent growth of normal cells.

When a fragment of embryonic mesenchyme 1 mm in diameter is placed in a layer of blood plasma 0.5 mm thick in a tissue culture, the cells in these fragments invade the medium, then grow and finally suffer a self digestion exactly as cancer cells suffer these changes in the body. As other studies have shown, these reactions are not reactions of the cell to specific substances in the plasma. They are the result of the removal of these cells from their normal circulation of blood in the organism to the stagnant culture medium that is well supplied with oxygen. The same reaction takes place readily when such a fragment is placed in a similar layer of pure isotonic sodium chloride solution. These reactions which these cells suffer are the result of a gradual accumulation in this stagnant environment of a substance or substances, the archusia (S). The proof of this deduction has been made by extracting actively growing tissues of the body and the same tissues before and after they have been placed and allowed to remain in the stagnant medium of a tissue culture. The archusia is formed only in the presence of nutrient substances and oxygen. It is the energy not only for growth but also for all other manifestations of life of the cell. In low concentrations (S¹) the archusia has no effect. In medium concentrations (S²) it causes the cells to migrate into a solid protein medium and toward larger droplets of fat. Smaller particles of proteins and small fat droplets are drawn in and stored in the cell. The connective tissue cells lay down intercellular substances under these conditions and other cells suffer their normal differentiation. In high concentrations (S³) of the archusia these proteins and fats are digested, the extracellular materials suffer degeneration and the cells grow and divide by mitosis. In all higher concentrations (S⁴) the cells themselves are digested.

² Wilson, E. B. *The Cell in Development and Heredity*, New York, 1925, p. 1030.

The changes, migration followed by growth and then self digestion, which the cells of a 1 mm thick fragment of a cellular mesenchyme suffer when placed in a small amount of stagnant culture medium are only the result of a gradual accumulation of the archusia in these stagnant cultures. If one changes any of those conditions which are necessary for the accumulation of the archusia all of these manifested changes in the cells are slowed or inhibited completely. The concentration of the archusia is directly proportional to the number of cells acting per unit area, the nutrient substances and the oxygen present and inversely proportional to the amount of absorbing medium diluting it. As the concentration of the archusia is thus lowered the first of these processes to disappear is self digestion, then growth, and finally migration fails. If smaller fragments of the same tissue are placed in the same layer of medium the amount of archusia formed per unit time is less. With this decrease the appearance of the self digestion and growth is delayed and migration is slowed. As the fragments are made still smaller self digestion finally disappears except in the most central cells of the fragment. Then growth fails and, finally, when single cells are scattered in the medium migration also fails to appear unless archusia has been brought to the culture with them or extracted from other sources and added to the medium.

The actively growing embryonic tissues are rich in archusia. Mesenchyme cells isolated from them stretch out to take a spindle or irregular stellate shape in the medium and then become inactive. When archusia is extracted and added to the medium in small amounts these cells not only show these changes but also migration. If more archusia is added they grow and divide and show evidences of self digestion. Most adult tissues contain little or no archusia. Fibroblasts isolated from such fragments remain inactive in the medium.

By changing the thickness or the amount of medium about these fragments without changing their oxygen supply these reactions can be slowed or increased at will. The medium absorbs and dilutes the archusia as it is formed. These reactions take place, therefore, much more readily in thin layers of medium than in thicker ones. By washing these cultures with a stream of serum these reactions can also be slowed and inhibited completely. They begin again after the flow of serum is stopped and the archusia (S) can accumulate again about them.³

Oxygen is absolutely essential for this whole reaction. Recently Drew,⁴ noting the self digestion in the centers of fragments of cancerous tissue in the body and in the centers of all fragments of tissues in the cultures about which growth takes place, thought this digestion

³ Burrows (Footnote 1 second reference)

⁴ Drew, A. H. *Brit J Exper Path* 4 46 (April) 1923

an autolysis resulting from an absence of oxygen, as Champy⁵ had originally described it. It is not an autolysis in any sense that we use the word autolysis at the present time. It is something that takes place in the presence of oxygen. It is the result of an excessive amount of the archusia about the cells. I have named it self digestion, therefore, to distinguish it from autolysis, which is the result of the absence of oxygen. Oxygen diffuses into clots of plasma no more than from 0.5 to 0.7 mm and no more than 1 mm into most tissue fragments. If one increases the thickness of the fragment or the layer of medium above these limits, the migration, the normal growth of the cells, and their self digestion is immediately inhibited. A true autolysis proceeds in the centers of the fragments and in all parts of it which lie beyond the limits of the diffusing oxygen. The toxic products diffusing from these autolyzing cells inhibit the reaction of cells lying in the zone of oxygen diffusion.

Warburg⁶ also has recently noted that less oxygen is absorbed and carbon dioxide given off by cancerous than by normal tissue. At the same time he finds an excessive breaking up of sugar to lactic acid in the cancerous tissue. He assumes, therefore, from these observations that cancer is the result of a reduced oxidation and that its energy for growth is derived from the fermentation of sugar. Smith⁷ in this country has advocated this view. As pointed out in the foregoing, an excessive amount of archusia such as is found in cancerous tissue leads not only to a splitting of sugar but to a splitting of the entire protoplasm of the cell. The archusia is formed by the oxidation of foods in the cell. It is well known from the "Law of Mass Action" that the velocity of such a reaction leading to the oxidation of food with the formation of the archusia is directly proportional to the concentration of the reacting substances (food and oxygen, in this case) and inversely proportional to the concentration of any one or all of the substances formed by the reaction. Carbon dioxide and the archusia are two of the products formed in this reaction. The carbon dioxide escapes, the archusia remains. As the archusia concentrates more and more this reaction must become slower and slower in the same proportion. Such an accumulation is found in cancerous and all growing and highly functioning tissues. The archusia escapes from the cells in the normal organism by way of the blood stream. The amount of oxygen used by the cells of the normal organism must be much higher, therefore, when these cells are isolated than that used by a cancerous tissue. I have found in the study of the growth, migration and function of normal embryonic cells in the cultures that oxygen is essential only for

5 Champy C L. *Rev gen d Sc* **24** 790 1913

6 Warburg, Otto. *J Cancer Research* **9** 148 (March) 1925

7 Smith, E. *Science* **61** 595, 1925

the formation of the archusia. In the presence of the archusia all the other reactions essential for these processes proceed without oxygen.⁸ The archusia is to the cell what the heat is to the steam engine. Oxygen is necessary for the steam engine only for the liberation of heat. The other reactions of the engine then proceed without oxygen.

Recently Barta,⁹ working in my laboratory and in other laboratories at Washington University School of Medicine, has shown that reduced oxidation does not stimulate growth in tissue cells but leads to the transformation of the cells into reticular and giant cells and to autolysis. These changes can be prevented by adding either oxygen to the cultures or archusia extracted from other sources.

Warburg attempts to strengthen his argument in favor of the view that the energy for growth in cancer is derived from the fermentation of sugar by showing that Meyerhoff¹⁰ had come to the same conclusion in regard to muscular contraction. As must be pointed out here, the facts brought forward by these authors in support of such a view are too few to warrant the conclusion. The facts I have enumerated in the foregoing disprove it. These fermentation processes which they describe are only secondary processes in the synthesis of protoplasm and the result of a high concentration of the archusia.

The same conditions that I have outlined above as necessary for the growth of normal embryonic mesenchyme cells are also necessary for the growth of other cells of the embryo, cells of adult animals and the cancer cells. The cells of these various tissues vary in their reactions only in proportion to their original archusia (S) content in the body. Cancerous and embryonic tissues are rich in this substance while adult tissues contain only traces of it. This difference in the amount of archusia in these tissues is not related to any peculiarity of the cells, but to the blood supply and to other conditions regulating its formation and escape from about the cells. The cells of the malignant tumors react in the cultures in proportion to their original growth rate in the body. The other difference between the cancer cells and those of the young embryo when placed in the cultures is that the cancerous tissues degenerate more quickly than the embryonal cells. I had wondered whether this difference might not be due to a greater quantity of nutrient substances in the embryonic tissues than in the cancers. In recent experiments in which these various tissues were fed to rats, we have found a greater quantity of vitamin A in the embryonic than in the tumor fragments.¹¹

8 Burrows, M. T. *Proc Soc Exper Biol & Med* **18** 133, 1921.

9 Barta, E. Unpublished data.

10 Meyerhoff, O. *Chemical Dynamics of Life Phenomena*, Philadelphia, 1924.

11 Burrows, M. T., and Forstad, L. H. On the Source of Vitamin B in Nature, *Am J Physiol* to be published.

Adult cells react the same but always after a longer latent period. The cells of adult connective tissue are widely separated by intercellular substances. They are like the fragments of the cellular tumors and of the embryo which have been teased apart. The longer latent period has been shown to be due to the small quantity of archusia which they contain in the body and to the presence of growth inhibiting substance (ergusia or vitamin A) in them. The actively growing embryonic cells and cancer are already rich in archusia when transplanted. The archusia does not reach S_2 concentration in the normal adult tissues, except in fragments of the skin, hair, bone marrow and the cells from other actively functioning and growing centers, until these fragments have remained for a time in the stagnant cultures. If these fragments are left for a long time in the stagnant culture medium and are then transplanted to fresh plasma they react after a short latent period as the cells of the cancers and the embryos¹². The latent period for the growth of the cells in fragments of actively growing cancer and embryos is evidently only the result of a temporary dilution of the archusia by the plasma of the culture which is free from it. The longer latent period of the inactively growing cells of the adult is the period necessary for the archusia to accumulate in the fragments suffering stagnation and for the plasma to remove the growth inhibiting substance from them.

When the archusia is extracted from other sources and added to the plasma of a culture it stimulates cells to grow. The embryonic and the cancer cells react more quickly to the archusia than the normal adult cells. The normal adult cells in their differentiation or long sojourn in an environment poor in archusia had undergone changes that inhibit their reaction. These changes are not irreversible. After these cells have remained for a time in the presence of the archusia they grow. If they are then removed in this growing state to fresh medium containing archusia they react quickly to it as the growing embryonic and cancer cells. The skin epithelium of the adult frog is a thin layer of cells. The cells are continuously growing in it. The cells have ceased to grow in the underlying connective tissue layer of the skin of these frogs. The epithelial cells show activity within from one to two hours after a fragment of skin is transplanted to a layer of plasma. The connective tissue cells under the same conditions will not react until after twenty-four, ninety-six or more hours. This activity of the epithelial cells can be inhibited entirely by stripping the epithelial layer from the underlying connective tissue and laying it in the plasma. The plasma in contact with both sides of the layer absorbs the archusia in it as fast as it is formed. The archusia cannot reach a concentration

12 Lambert, R. A. *J. Exper. Med.* **17** 499, 1913

in the layer sufficient to induce activity in the cells. If, on the other hand, one rolls such a layer into a compact mass the cells show migration.

From these observations I was forced to believe that body cells are not fundamentally different from unicellular life in general in nature. It is in the stagnant pool and not in the running stream that such life abounds. Cellular growth in the animal body is most active in the early periods of development. It wanes and ceases as the blood vascular system develops and the cells become separated by this active blood flow except in certain regions, skin epithelium, hair, nails, sex glands and bone marrow, in wounds, tissues suffering hypertrophy and hyperplasia and in cancer.

In previous articles¹³ it has been shown that growth in each of these places or under each of these conditions is associated with a stagnant circulation and an overcrowding of cells. This stagnation and overcrowding is greatest in cancer.

These facts had led me to believe that cancer may be nothing more than the result of a local crowding of cells and a relative reduction in the blood supply to the mass. In proof of such a conception it has been possible to show

1. The various substances and conditions known to be able to induce cancer, such as coal tar, other lipid solvents, roentgen rays, radium, animal parasites, bacteria, chronic inflammation, congenital defects and anomalies, act only to produce such a tissue organization. We have shown that coal tar¹⁴ and other lipid solvents¹⁵ have no stimulating value for the cells. Drops of coal tar and many other oils placed in the tissues cause the cells to degenerate. In so doing they also attract cells to them from wide areas of the tissue about them. These drops become encapsulated by a dense mass of cells. This action of coal tar is always limited. While many of the cells degenerate in this capsule others remain intact and recuperate readily after the action of the tar has ceased. If sufficient cells have accumulated an active growth of them intervenes in this stagnant environment and cancer develops. If fewer cells are accumulated the connective tissue cells lay down intercellular substances⁸ and the epithelial cells proliferate for a time but eventually the whole reverts to a hyaline scar¹⁶.

Animal parasites and bacteria produce this dense mass of cells largely free from blood vessels by stimulating directly through their own archusia an active local proliferation of cells without the formation

13 Burrows, M. T. J. *M. Res.* **44** 643 (Sept.) 1924, Footnote 1, first and fifth references.

14 Jorstad, L. H. J. *Cancer Res.* **9** 232 (June) 1925.

15 Burrows (Footnote 1, fifth reference).

16 Burrows, M. T., and Johnston, C. G. J. *Exper. Med.* **42** 215 (Aug.) 1925.

of blood vessels¹⁵ Roentgen rays and radium¹⁷ disturb the blood vascular supply as well as increase the metabolism or the production of archusia in the cells exposed

2 In other experiments¹⁸ it has been shown that any dense mass of cells not only grows readily but also destroys any neighboring less dense mass of cells as cancer destroys the normal tissues about it. In this destruction the blood vessels as well as other tissues suffer. Thus any dense mass of cells once established in the organism must continue to grow indefinitely in that it can reproduce its own stagnant organization through the destruction of normal tissues and blood vessels about and within it.

3 The third proof of this conception is found in the close similarity in the growth of cells in a tissue culture to that in cancer. As is well known and as has been pointed out in previous articles the cells in a tissue culture do not grow to form organ structure but invade the medium and grow in it as cancer invades the organism. The conditions that allow these cells to grow independently in this manner in the cultures are stagnation and cell crowding, as has been shown in previous articles and outlined in the foregoing.

In this paper it became of interest to see if this analogy could be carried further and whether cancer metastases can be explained on the same basis. The problem of metastasis is the problem of the mechanism of the migration of these cells and their ability to grow and form new tumors by this growth in parts removed from the original tumor.

One of the strongest arguments that has been raised in support of the view that the cancer cell is different from the normal cell is that it can invade the tissue, migrate to distant parts and form metastatic tumors. There is no evidence that under normal conditions the epithelial or other of the fixed tissue cells can perform these acts. The question therefore arises, Can these acts be resolved to the same conditions of overcrowding and stagnation, or are they something peculiar to a specifically differentiated cancer cell or to some parasite or other agent, as certain English and American authors are now attempting to prove?¹⁹

The earlier work on the tissue culture had already shown that the mechanism for migration of normal cells that are crowded in densely cellular fragments in the tissue culture is not the same as that of the same cells when they are transplanted in smaller fragments. Harrison,²⁰

17 Burrows, M. T., Jorstad, L. H., Lunsford, C. J., and Ernst, E. C. Paper read before the Internat. Congr. Radiology, London, July, 1925.

18 Burrows (Footnote 13, first reference).

19 Nuzum, J. W. Surg., Gynec. & Obst. **4** 343 (March) 1925. Ochsner, A. J. Ibid. **40** 336 (March) 1925. Gye, W. E. Lancet **2** 109 (July 18) 1925. Barnard, J. E. Lancet **2** 117 (July 18) 1925.

20 Harrison, R. G. J. Exper. Zool. **9** 787, 1910.

in his earlier attempts to observe a growth of nerve fibers from fragments of the neural tube of frog embryos, placed these fragments of the nervous system in hanging drops of serum. No growth was observed. Success was attained only when he placed the fragments in drops of lymph which clotted to form a solid medium. It was into this solid medium that the nerve fibers grew and the cells migrated. He notes that the nerve fibers grew out and the cells migrated always in contact with the fibrin fibrilli of the clotted lymph. Harrison therefore concludes that these cells are stereotopic and that solid support is a necessary factor for their migration and growth.

In developing a more general method for culturing cells of higher animals, I used blood plasma as medium. The plasma clots to a solid gel when the tissue cells are added to it. Into this medium it has now been found that all types of cells of adult and embryo may migrate readily.

In 1911, M. R. and W. H. Lewis²¹ observed an active migration and growth of cells from fragments of tissue of chick embryos into hanging layers of simple physiologic sodium chloride solution and other liquid mediums and serums.

Harrison²² repeated these experiments of the Lewises to find that the cells did not migrate directly into hanging drops of these liquid mediums, but they moved always along the cover glass or lower free surface of such hanging drops. I also studied these cultures of the Lewises. I found that only the cells from actively growing and densely cellular fragments of tissue can migrate and grow in this medium.²³ The cells from similar fragments of older embryos and adults cannot migrate unless these cells have been previously brought to an actively growing state by replanting fragments of them in drops of plasma.

It was also noticed that when one reduces the size of the densely cellular fragments of the younger embryos and of cancer and separates the cells slightly within them that these cells also cannot migrate nor grow in a liquid medium. In plasma the cells of the same small fragments migrate readily but they do not grow. In comparing the behavior of the same large and small fragments in both a liquid medium and plasma, it was interesting to note that when one reduces the size of a fragment of mesenchyme so that its cells fail to grow in equally thin layers of plasma that they also simultaneously fail to migrate along the surface of a liquid. When the fragment is large enough for the cells to grow readily in the plasma they are then able to migrate and grow along the surface of a liquid medium.

21 Lewis, M. R., and Lewis, W. H. *Anat. Record* **5** 277, 1911.

22 Harrison, R. G. *Science* **34** 279, 1911.

23 Burrows, M. T. *Anat. Record*, 1917, p. 335, *J. Cancer Research* **6** 131 (April) 1921.

These facts had led me to study more carefully the migration of mesenchyme and epithelial cells from the large and the small fragments into plasma clots. From the smaller fragments the cells migrate directly into the plasma clot. The clot contracts ahead of them and becomes transformed into fibrin. The cells cling tightly to these fibrin fibrils. This migration is most rapid at first. It slows gradually as the cells become more and more separated. Eventually these cells come to rest and lie intact but inactive for an indefinite period. During this migration they have shown no growth but have decreased in size except as they have suffered swelling from the fat droplets they have accumulated in their cytoplasm.

About the larger densely cellular fragments the picture is different. The first cells to appear enter the clot. Most of these then soon leave the clot to move on one or the other or both of its surfaces. In the clot the mesenchyme cells have a slender spindle shape. Their boundaries are sharply defined. Their nuclei are seen with difficulty except when they are stained and their cytoplasm contains fat droplets. On the surface of the medium they often contain no fat. They are flattened to spindle or polygonal shaped plates. Their nuclei become visible, occupying their entire vertical axis, and their edges become indistinct. These cells in this position grow rapidly, divide by mitosis, show an early vacuolization of their cytoplasm and later suffer a self digestion (Fig. 1).

At an earlier time I had already studied the mechanism of migration of these cells from these two sized fragments. The results of this work are reported in another paper²⁴. Body cells, unlike ameba and many unicellular organisms, migrate only in straight lines away from a fragment and other cells. In this migration they may or may not show any ameboid movements. From the smaller fragment the migration of these cells is entirely the result of their liberating a soaplike substance that is absorbed only by proteins, fats and other similar substances. It is insoluble in water and does not decrease the surface tension of water. This substance liberated by the fixed tissue cells also coagulates fibrinogen to fibrin. It is readily absorbed by the fibrin and decreases the surface tension of the cell in contact with the fibrin. The cell is thus stuck to the fibrin and moves in the line of the diffusion of this soaplike substance. This soaplike substance I have called the *ergusia* or the laboring substance of the cell. It is also readily absorbed by fats. Smaller particles of proteins and small fat droplets are drawn into the cell by it while the cell moves into protein

24 Burrows, M. T. *Energy Production and Transformation in Protoplasm as Seen Through a Study of the Mechanism of Migration and Growth of Body Cells*, to be published in *Am. J. Anat.*, 1925.

clots which are attached to rigid bodies without and toward and against large fat droplets having a greater inertia than themselves

The ergusia is not liberated by the cell under all conditions, but only when the archusia reaches an S_2 concentration. The effects of the liberation of the ergusia are seen about the smaller fragments, but fail the cells completely isolated in a clot unless the archusia (S) is added from other sources

Under the influence of a greater crowding of the cells and the S_4 concentration of the archusia which results, the whole picture of activity in the cell changes. It digests the proteins and fats of its environment and absorbs water rapidly. Under the influence of an S_4 concentration the cell is digested

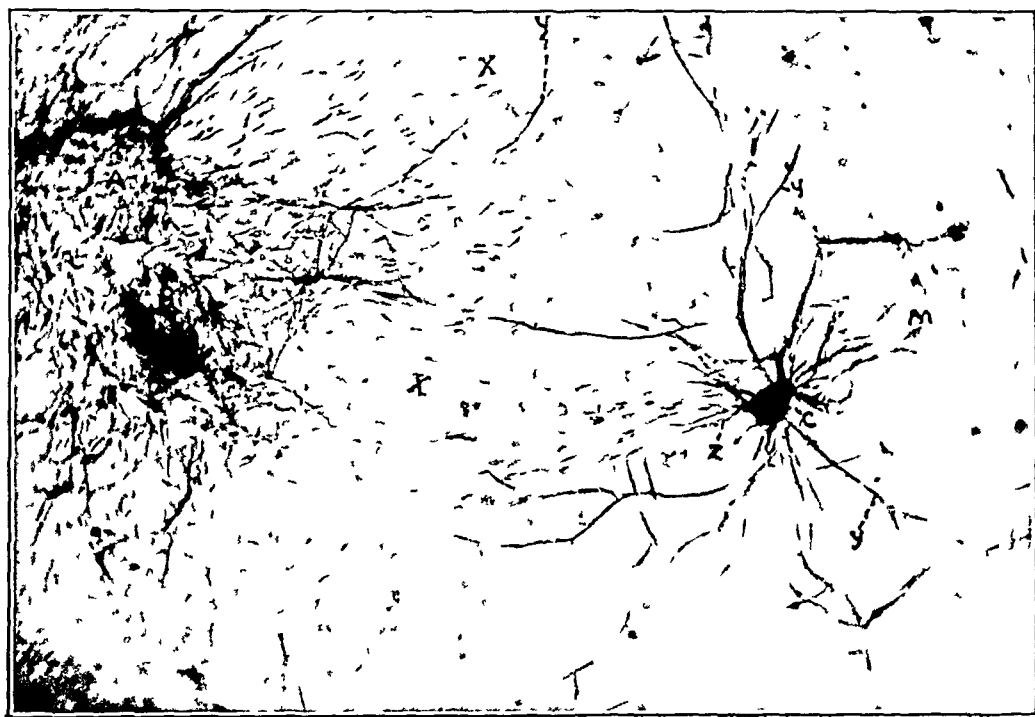


Fig 1—Culture of fragments and isolated cells of heart of 10 day old chick embryo in medium of plasma prepared from blood of adult chicken, fifteen hours after the chicken had eaten, three fragments and a few isolated cells are shown. The culture was 48 hours old when it was fixed in formaldehyd and stained with Delfield's hematoxylin. The plasma layer was originally 0.3 mm thick, the larger fragments were originally 0.3 mm, and the smaller one was a little more than 0.1 mm. The larger fragments, A and B, show the typical reaction of all the larger cellular fragments of tissue in the cultures. The cells in the center of these fragments have suffered a self digestion and the liquid liberated in this self digestion has spread over the surface of the plasma layer. The border cells of each of these fragments have moved out and dispersed into the clot and into this surface film. In the film they are flattened and stain less sharply, X, in the plasma they are slender spindles and more compact, Y. No surface film has formed about the smaller fragments, C, its cells are moving into the clot. The surface film from the larger fragments passes under this smaller one. Where the cells from the smaller fragment have become caught in this film they have flattened Z, and one of these cells in this film is dividing, M.

In this digestion we noted that a liquid substance is liberated. This liquid is also insoluble in water but, quite different from the ergusia it decreases the surface tension of water. It flows readily over the surface of salt solution or plasma. In the cultures in which salt solution and liquids had been used as medium the cells had not migrated into the liquid medium nor in contact with it, but into this liquid film which had spread from the fragments. The cells in the centers of the larger fragments had suffered an early self digestion²⁵. These films are only the result of an overcrowding of the cells in the centers of the fragment or an excessive accumulation of the archusia (S) in this region. In these cultures all of the cells which migrate do not reach the surface films. A few of them remain in the plasma clot (Fig 1). These cells as they move farther out finally come to rest as the cells migrating from the smaller fragments. The cells which grow at a distance from the fragments in the cultures are only those cells which are bathed with an excessive amount of archusia carried in the special surface films liberated by the cells digesting in the central parts of the fragment. The cells which had migrated into the clot are not different from those on the surface. If one removes them to the surface film they flatten as the other cells flatten, grow, divide by mitosis and later suffer the self digestion.

These conditions, which are necessary for the growth of the normal cells, are also absolutely essential for the growth of the cancer cells in vitro. When one reduces the size of the fragments of cancer and separates the cells in them so that the cells in the center of these fragments fail to suffer self digestion and liberate the substances that form the films, these cells cannot migrate along the surface of a liquid. They migrate into a plasma clot but as they separate from each other and their archusia has become diluted about them they come to rest exactly as the normal cells come to rest under these conditions (Fig 2).

In the normal adult organism the concentration of the archusia as shown by extractions does not exceed a concentration of S^2 except in the few growing areas, bone marrow, sex glands, skin, nails and hair. In these regions it is barely S^3 . No self digestion of cells is seen under normal conditions except in certain periods of early embryonic life. The pronephros and metanephros suffer such a digestion. In cancer conditions are different. The archusia is always S^3 and S^4 in this tissue. This high concentration of the archusia is due to the fact that the cells are overcrowded in this region and their circulation is greatly impaired. The central parts of the cancer suffer the same self digestion as that seen in the larger compact fragments of the culture.

In the plasma clot the cells from the smaller fragments can migrate only until the clot becomes saturated with the ergusia. The intercel-

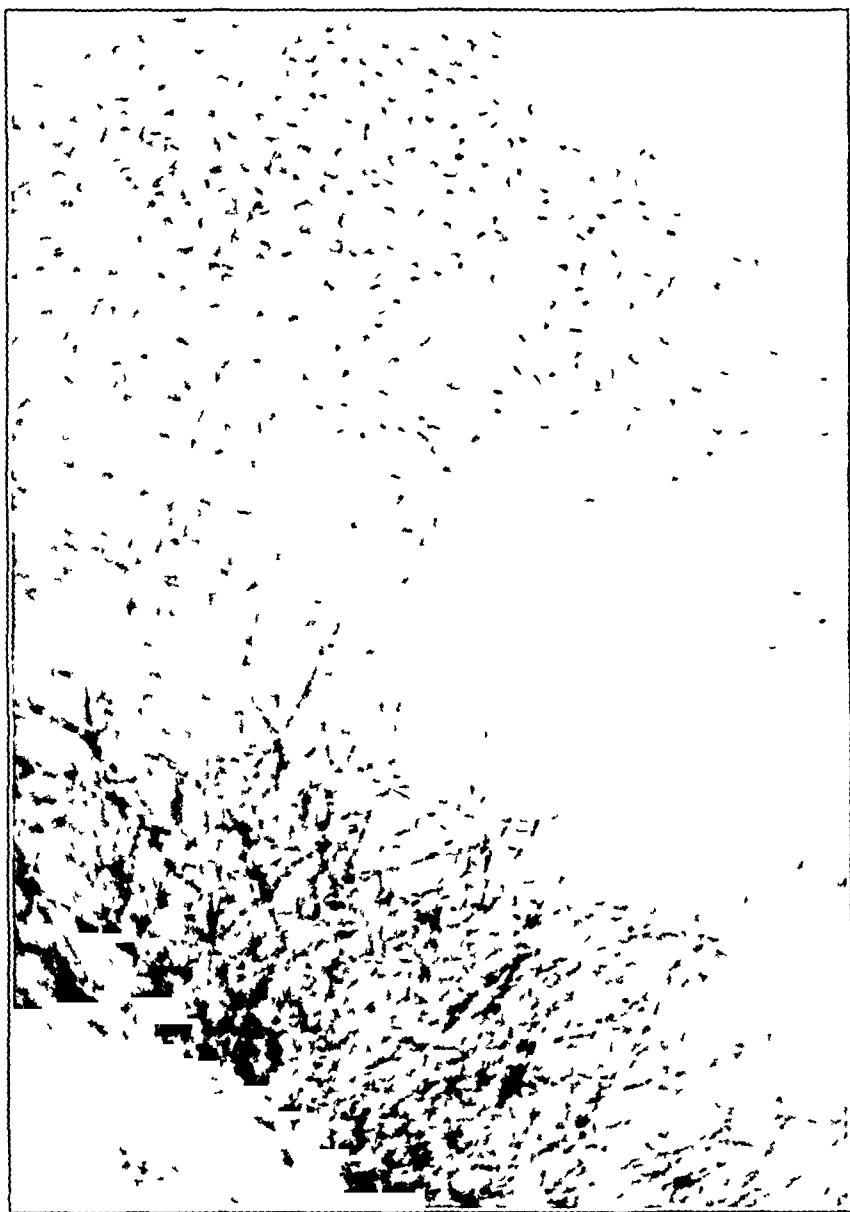


Fig 2—Culture of fragment of Rous chicken sarcoma in plasma prepared from blood of normal adult chicken, the culture was fixed in formaldehyd and stained with Delfield's hematoxylin when 72 hours old. The picture shows one edge of the fragment. The fragment was originally 1 mm in diameter and the plasma layer 0.5 mm in thickness. The central cells of the fragment have undergone a self digestion and liquefaction. A film of fluid has moved out over the lower surface of the clot of plasma. The tumor was originally a round cell type. The border cells of the fragment have moved into the clot and into the film of fluid over the lower surface of the medium, in the clot they have reverted to a spindle cell type and have ceased to grow. In the surface film they have remained as round cells, those near the fragment are degenerating, those farther out are growing. As many as five mitoses may be seen in a single low power field in this region. Even the cells of this tumor of Rous, which contains special stimulating substances unknown to human cancers and to other cancers of chickens and of other animals, respond to the same conditions and in the same manner as normal cells.

lular substances of the body are so saturated. Into a wound fresh plasma exudate has been exuded. The cells migrate readily into this exudate. They grow in this stagnant area until their circulation has been reestablished.¹³

The question arose, Are metastases the result of the same conditions? In the cultures it has been noted that this fluid liberated in the centers of the fragment spreads as readily over the surface of a plasma clot as over the surface of salt solution. When it spreads over the surface of a drop of salt solution it makes this surface leathery so that it cannot be made to run easily when the slide is tipped on which it is lying. It is a fluid, therefore, which can decrease the surface tension of water much more than any fluid known to exist in the normal organism. It should therefore be able to flow readily over the surfaces covered by differentiated cells of the body. In proof for this last possibility it was found that it can flow readily over the surface of a plasma clot filled with ground normal tissues and over neighboring fragments of normal tissues placed in the culture medium. Cells coming from these normal fragments and caught in these films eventually grow and divide by mitosis (Fig. 1).

In the body metastasis of cancer takes place along the surface of the lymphatics, blood vessels and other tissue surfaces or by way of the blood stream to distant organs. Their chief course is always, however, along the lines of surface drainage from the original tumor mass.

It therefore became of interest to see if these streams of fluid preceded the spread of the cancer cells in the organism. One of the chief means of testing for the existence of this fluid is its ability to stimulate growth in normal cells. I have looked for the existence of this growth stimulating fluid in the blood stream of patients with generalized and extensive metastases and in the lymph glands and other tissues about cancers previous to the spread of their metastases.

CHANGES IN TISSUES ABOUT DEVELOPING CANCERS

During recent years a large number of patients with early cancer of the lip, breast, other areas of the skin, genitals and internal organs have entered the clinic. It has been the experience of the clinic that simple removal of these tumors, except certain of the basal cell cancers of the face and of the extremities, does not effect a cure. The glands draining the cancerous regions must also be removed. This has given us a wealth of material to study the early changes in the lymph gland and other tissues about these tumors. I have collected the specimens from 400 of these tumors. In this group there are 360 carcinomas, thirty-two sarcomas and eight melanomas. Most of these tumors were from 2 to 6 months old. Others had endured for no more than a month before operation.

In every case the picture was the same. There is marked hyperplasia of the endothelial cells lining the lymph vessels draining the cancer and similar extensive hyperplasia of the lymph glands into which these vessels drain. In the lymph glands this hyperplasia begins along the periphery of the entrance of the afferent vessels. It involves not only the germinal centers but also the whole of the gland. The endothelial cells lining these afferent vessels have proliferated. They are no longer a thin layer of flattened cells, but appear now as a closely set layer of cuboidal cells, one to several in thickness. The same proliferation is seen in the cells lining the sinuses of the gland. In

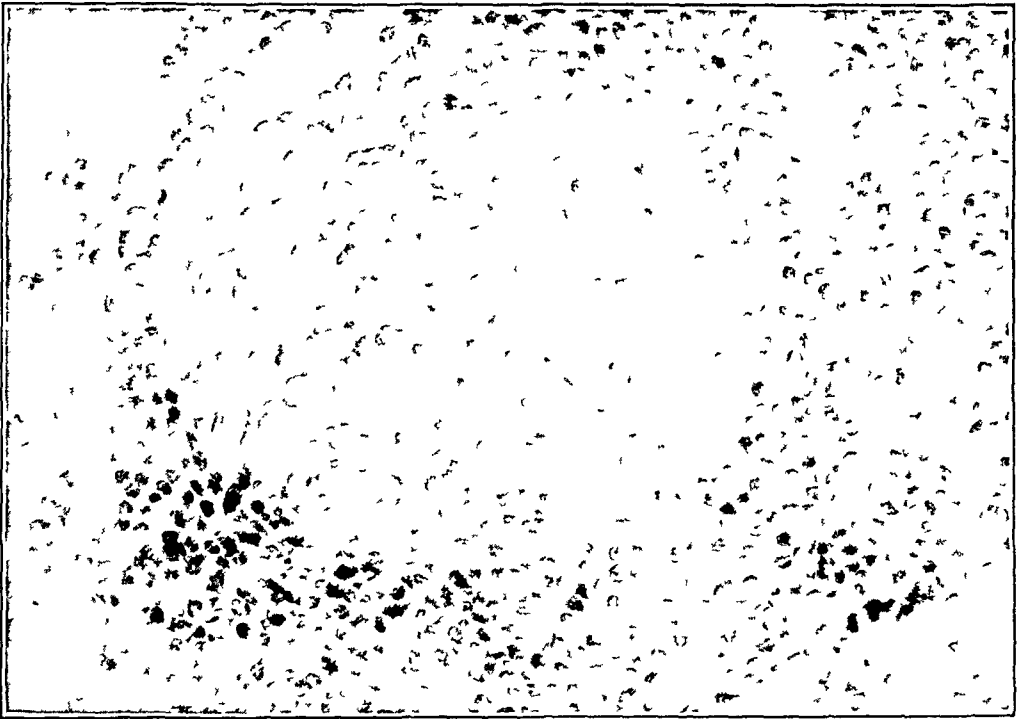


Fig 3—Section of gland of neck draining material from a cancer of the jaw, under moderately high power, the picture includes a small follicle showing mitoses, there are mitoses also in the cells of the surrounding glandular tissue

many places this proliferation has proceeded until the whole sinus is filled with these cells. The germinal centers have increased greatly in size. In the earlier stages they appear as a dense mass of cells. Later the centers of these masses degenerate and clear. This makes them stand out prominently in the stained specimen. Mitotic figures are seen in all parts of the gland. They are especially prominent in the germinal centers (Fig 3). In this region the cells degenerating show exactly the same appearance as the normal cells growing, dividing and degenerating about any densely cellular fragment of normal tissue placed in a tissue culture.

This hyperplasia is seen in the glands draining every cancer. It is as common in the glands draining melanomatous and sarcomatous tis-

sue as in those draining fluid from a carcinomatous tissue. In many of the older subjects these glands had atrophied and become replaced by a large mass of fat. This fat fills their lumen and central parts. In these cases the cells proliferate first along the circumference and gradually remove the fat as they grow and increase in number.

The picture of hyperplasia in the lymph glands of cancer that I have given is not new. It has been observed and described by previous authors.²⁶ Its significance has become possible of understanding, however, only in the light of the studies of the conditions regulating the growth of normal cells as portrayed by the tissue culture.

It is into these hyperplastic glands that the cancer cells invade and grow to form new tumors. The growing lymphoid cells are then rapidly destroyed by the loss of their substance to the cancer cells. The cancer cells predominate in most of these cases merely because they have become adapted to respond more quickly to these stimulating substances than the other normal cells. This need not, however, be the case. There are numerous instances in the literature in which the normal cells have undergone malignant transformations at a distance from the cancers. L. Loeb and also Lewin²⁷ report cases in which the skin epithelium of a normal rat underwent malignant transformation in the neighborhood of a transplanted cancer. Malignant transformation of the stroma of both transplanted and human cancers is well known. I succeeded in inducing a cancer in the skin of a rat by reducing the circulation of the skin by pressure and injecting fragments of embryo rat plus a Berkefeldt filtrate of a Jensen sarcoma. The Berkefeldt filtrate of the Jensen sarcoma of the rat unlike that of the Rous chicken sarcoma will not induce tumor when injected into normal tissue.²⁸

It is easy to induce a growth of the cells in a fragment of normal tissue too small for them to grow when it is isolated in a drop of plasma by placing it near a larger fragment even when the cells of the larger fragment are not able to grow. The archusia from the larger fragment uniting with that of the smaller fragments leads to a digestion of the cells in the center of the smaller fragment, a surface film, an invasion of the medium, and a growth of the border cells of the smaller fragment.

CHANGES IN THE BLOOD OF CANCER PATIENTS

Several authors have noticed an alkalosis of the blood of cancer patients. The significance of this had never been investigated. It was interesting, however, in going over the literature on this subject to notice that although the alkalosis was often considerable that these patients

26 Ewing, James. *Neoplastic Diseases*, Ed 2, Philadelphia 1922, p 78.

27 Loeb, L., and Lewin, cited by Burrows, M. T. *J. Missouri M. A.* **20** 145, 1923.

28 Burrows (Footnote 27)

never showed any evidence of tetany. The question that arose was: Is this alkalosis due to a change in the carbon dioxide-bicarbonate ratio or to the addition to the blood of other substances? I asked Dr. Chambers²⁹ to investigate this question. Using the indicator method on dialysates of the blood of these patients he found no evident alkalosis in the early stages of cancer. As the cancer advanced and metastasis appeared the alkalosis appeared and became more and more pronounced as the metastasis spread to distant parts. According to his results the dialysate of normal persons has a p_H of 7.3 while in many cases of cancer with liver metastasis it reached a value of 7.6. There was no difference apparently between carcinomas, melanomas and sarcomas in this regard.

Having established this fact, Chambers then studied the carbon dioxide-bicarbonate ratio in these cases. He found it always normal. Evidence of an alkalosis was found only in the dialysate. It was not the result of changes in the carbon dioxide-bicarbonate ratio but evidently the result of the addition of some acid protein substance to the blood which could not pass through the celloidin sacs with the hydrogen ions with which it had combined.

OTHER STUDIES ON THE BLOOD OF CANCER PATIENTS

In recent years many students of the tissue culture have described stimulating substances in the blood of cancer patients. In most instances this work has not, however, been reliable because no controls were made of other conditions that might change the growth of cells in a normal plasma. Our results of these studies have been more or less irregular. In general it has been interesting to note that the blood plasma of patients with advanced cancer stimulates the cells more than normal bloods.

One difficulty that arises in making these tests is that fat in the blood inhibits the growth of cells in it. The cancer patients suffering anemia have a higher fat content in their blood than normal patients. This fat can be decreased by starving. I have attempted through short periods of starvation to equalize the fat in the blood of animals with cancer with that of normal animals. In such experiments a definite stimulating value has always been found in the blood of cancer animals (rats). When the blood is taken without respect to eating and fat content the results have always been irregular. This stimulating value in the blood plasma of the cancer animals is greater in the blood from those animals in which the cancer is metastasizing.

The experiments on man have been equally difficult. In these studies I compared the growth of embryonic chick tissue, human can-

²⁹ Chambers, W. H. *J. Biol. Chem.* **55**, 229 (Feb.) 1923. Chambers, W. H. and Kleinschmidt, R. E. *Ibid.* **55**, 257 (Feb.) 1923.

cerous tissues and normal tissues taken from arteries removed at hernia operations on children and young men. These tissues were cultivated in bloods of normal men under normal conditions and after they had starved themselves for from twelve to twenty-four hours, patients with acute infections (pneumonia and typhoid fever), alcoholic patients recovering from a period of drunkenness, patients with chronic tuberculosis and cancer patients. Starvation of moderate degree makes the blood plasma a much more efficient medium. The plasma prepared from the blood of the acutely ill patient and the alcoholic patient is toxic. The blood of cancer patients is always a good medium. In summing up our results it was found to be in general always better than the others.

As must be pointed out here, the process of growth is not merely the result of the action of the stimulus, the archusia, but depends also on the presence of other food substances in the medium. The stimulus acts only to change the protoplasm so that it attracts the necessary substances for growth into the cell, the proteins, the fat, the carbohydrates, the water and the salt. It then induces chemical changes between them and protoplasmic synthesis. Each of the various cells that compose the body, the liver cells, the muscle cells, the brain cells, differ from each other in their chemical and physical make-up. For them to grow they also must each demand more or less specific substances and other specific conditions.

For metastasis to localize in distant organs or tissues these points of localization must not only be sites where the circulating stimulus can collect, but they must also contain an ample collection of other nutrient substances for the growth of the cells.

It is not surprising, therefore, that in generalized metastases we find certain cells tending to metastasize only into certain regions and that we find certain organs immune from such metastasis in many persons.

COMMENT AND SUMMARY

From the foregoing observations it became evident that metastases in cancer are not the result of a simple migration of cancer cells from the cancer to distant organs. Metastases are primarily the result of the spread of a liquid substance from the main tumor mass. This substance spreads over surfaces. It is liberated through a digestion of cells in the center of the mass of cancerous tissue. This digestion is not an autolysis resulting from the absence of oxygen, but the result of an excess of the growth stimulating substance, a product of the cell's oxidation. This fluid is rich in growth stimulating substance. This fluid stimulates not only the cancer cells to grow but also the normal cells. The cancer cells already adapted to it respond more quickly. In their growth they then remove the nutrition and necessary substances from the other cells and destroy them.

This type of reaction may not always occur. As is well known the normal tissue may undergo malignant transformation. Such has been seen frequently in transplanted cancers of animals. These transformations are the result of a sufficiently long action of this fluid.

While these observations are interesting in throwing light on the nature of the mechanism of cancer metastases their greater importance is the more absolute proof they give for the cause of cancer.

In 1920 when we began to study the cause of cancer intensively at the Barnard Hospital, it had been shown that cancer can be induced by any one of a number of substances and conditions, such as coal tar, other lipid solvents, bacteria, animal parasites, roentgen rays, radium, arsenic and other substances. In man as well as in animals it is a disease of old age and may occur not only through the action of any one of the substances mentioned in the foregoing but also in congenital tumor and defects, in old chronic inflammatory areas, in tissues suffering atrophy from old age and tissues forced to atrophy from various external factors, such as exposure to sun and weather.

While animal experiments had shown definitely that any of the substances or conditions mentioned in the foregoing can induce cancer the same experiments had also shown that the same substances are not concerned or necessary for the subsequent growth of this disease. Cancer once induced by coal tar grows indefinitely to the destruction of the host without any further additions of this substance. Many cancers induced by coal tar have been transplanted to other animals and have continued to grow as actively as ever long after the tar has disappeared.

It became evident from these observations that cancer is not the result of any specific substances or group of substances. It is the result of some primary change either in the cell or the tissue which may be induced by any one of a number of widely different substances and conditions.

In view of the fact that no one had been able to show that the cancer cell is different from any other cell and that cells can grow in a tissue culture in a medium of the blood plasma of the body only when they are crowded in considerable numbers into a small amount of this medium, which is well supplied with oxygen, the question arose: May not cancer be only the result of cell crowding and stagnation in the body?

To assume that cancer is the result of irritation and then the invasion of a parasite was not possible in the light of any known facts. It therefore became of interest to study the action of the various substances in inducing cancer. It was found that each acts only to induce the formation of a dense stagnant mass of cells having a reduced blood supply. Drops of coal tar produce such a tissue organization by attracting the fixed tissue cells to them and crowding them about their peri-

pheres Bacteria and animal parasites when introduced into the tissues stimulate the cells to proliferate without the formation of blood vessels and intercellular substances Roentgen rays decrease the blood supply and also stimulate the cells

The question that concerned us, therefore, was whether metastasis as well as the independent growth of cells can be explained by the same cell crowding and stagnation In previous work it has been noted that cells of large, densely cellular fragments can migrate along the surface of a medium independent of any specific absorbing substances in the medium They accomplish this by the fact that a liquid is liberated from the centers of these larger fragments This liquid can flow over any water surface The cells move into it In this article it has been possible to show that such a fluid precedes the spread of cancer cells and metastases in the organism It has thus been possible to give practically absolute proof for the foregoing deductions of the nature of cancer by showing that the whole phenomenon can be reproduced by simply cutting down the blood supply to a cellular tissue and allowing the cells time to revert from the differentiated to the growing state

CHRONIC AND ACUTE ARTERITIS OF THE PULMONARY ARTERY AND OF THE PATENT DUCTUS ARTERIOSUS

KARL SCHLAEPFER, M D

MILWAUKEE

The association of a congenital cardiac anomaly and an inflammatory process of the heart valves is well known. A congenital anomaly of the heart with inflammation of the pulmonary artery with or without valvular endocarditis, however, is unusual. The object of this article is to record an instance of pulmonary arteritis with thrombotic occlusion of the pulmonary bulb and the patent ductus arteriosus in a child aged 8 years. This particular association of arteritis with a congenital cardiac anomaly is unusual, as shown in the following survey. The accompanying table includes nineteen cases of patent ductus arteriosus with arteritis of the pulmonary artery. In only three of these (Krzyzkowski,¹ 1902, Hamilton and Abbott,² 1914, Schlaepfer, 1926) were the heart valves intact and the inflammatory process restricted to the pulmonary artery and the ductus arteriosus. In the remaining sixteen cases a valvular endocarditis was present in addition to the inflammatory lesion encountered in the pulmonary artery and in the patent ductus arteriosus.

Four observations not included in the foregoing, published by Rauchfuss,³ on infants from 1 to 2½ weeks of age must be mentioned. The author correlated the thrombosis, which in these cases was confined to the patent ductus arteriosus, with "puriform thrombi" found in three instances in the vessels of the umbilical cord. The fact that a thrombus was present in the ductus arteriosus together with a blood stream infection made these observations seem worth recording.

REPORT OF CASE

A. F., a white boy, aged 8 years, was sent to the outpatient department of the New Haven Hospital in June, 1924, by the school nurse for a "weak heart." The family history was unimportant.

It is noteworthy that the patient never had rheumatism, whooping cough and measles were the only diseases of early infancy. Until June, 1924, neither

¹ From the Brady Laboratory of Pathology and Bacteriology, Yale University School of Medicine, New Haven, Conn.

¹ Krzyzkowski, J. Aneurysma des Stammes der Pulmonalarterie und multiple Aneurysmen ihrer Verastelungen bei Persistenz des Ductus Botalli, Wien klin Wchnschr **4** 92, 1902.

² Hamilton, W. F., and Abbott, Maude E. Patent Ductus Arteriosus with Acute Infective Pulmonary Endocarditis, Tr. A. Am. Phys. **29** 294, 1914.

³ Rauchfuss, C. Ueber Thrombose des Ductus arteriosus, Virchows Arch. f. path. Anat. **17** 376, 1859.

family nor patient were aware of any abnormality. At the dispensary, a diagnosis of patent ductus arteriosus was made based on the following findings:

The left border of the heart was found 0.5 cm within the nipple line and an impulse was felt in the fifth intercostal space. A suggestion of a thrill in the pulmonic area was noted. The sounds were of good quality. A loud rumbling murmur in the pulmonic area replaced entirely the first pulmonic sound. The second sound was accentuated.

The child was kept under observation in the outpatient department but no untoward symptom arose until December, 1924, i. e., six weeks before admission to the hospital, when examination of the ears revealed dullness and injection of both ear-drums. Two weeks later the boy developed a "cold", the ears discharged, fever developed, the child became bedridden and complained of pains in several joints.

He entered the New Haven Hospital, Jan. 22, 1925. Physical examination now revealed marked dyspnea and inspiratory retraction over the supraclavicular fossa and below the xiphoid process, a perforated right ear-drum, a slight enlargement of the heart toward the left at the apex, a soft systolic and a faint diastolic murmur over the whole precordium, and a continuous murmur at the base. The temperature was 40.2 C, the pulse rate 120, and the respiration rate 54 per minute. The red blood count was 3,632,000 with 80 per cent hemoglobin, the white cell count, 22,400 with 83 per cent polymorphonuclear leukocytes, there were numerous colonies of *Streptococcus viridans* from the blood.

The illness progressed rapidly. The temperature became septic in type. Repeated cultures from the blood revealed numerous colonies of *Streptococcus viridans*. Petechiae were never present in the skin. Finally, the cardiac murmurs were obscured by gallop rhythm and the boy died within two weeks.

The clinical diagnosis was congenital heart disease, rheumatic heart disease, endocarditis, septicemia caused by *Streptococcus viridans* and bronchopneumonia.

The postmortem examination was performed four hours after death. The primary anatomic diagnosis was patent ductus arteriosus, hypertrophy of the heart, organizing and acute arteritis of the pulmonary artery and ductus arteriosus with thrombotic occlusion of the pulmonary bulb and ductus arteriosus, multiple infarcts of the lungs and of the spleen, and chronic splenic tumor. The subsidiary diagnosis was fibrous pleurisy and double ureter.

The bacteriologic diagnosis was *Streptococcus viridans*.

At necropsy the body was that of a fairly well nourished white boy. The skin and the sclerae had a yellow tint. No hemorrhages were noted in the skin.

Detailed drawings of the heart facilitate the description of the points of particular interest. The pericardial sac had no increased fluid. The epicardium was everywhere smooth and glistening. The estimated weight of the heart was 70 Gm. The right auricle and the right ventricle were dilated, the left heart was contracted. An irregular fusiform dilatation of the stem of the pulmonary artery was conspicuous (Fig. 1 A) commencing sharply about 1 cm above the pulmonary valve. The foramen ovale was closed. The tricuspid valve measured 7 cm in circumference, the cusps were thin and velamentous. The wall of the right ventricle was 3 mm thick. The pulmonary ring measured 5.5 cm in circumference. The leaflets were thin. Just above the attachment of the leaflets, the stem of the pulmonary artery was filled and distended by a gray-white and red, firm thrombus with irregular surface (Fig. 1 A). This clot extended into both main branches of the pulmonary artery and also occluded the patent ductus arteriosus (Fig. 2 A), but did not extend into the aorta. The duct was 7.5 mm long and 2.5 mm wide. The thrombus was firmly adherent to the vessel wall except in the left posterior aspect of the pulmonary artery where the intima was smooth. The thrombus was not adherent to the wall of the ductus arteriosus except at its pulmonary orifice (Fig. 3). The mitral valve



Fig 1—Anterior view of stem of pulmonary artery occupied by a thrombus irregular fusiform dilatation of pulmonary bulb should be noted, *A* lower end of thrombus and intact pulmonary valve are visible



Fig 2—Posterior view of dilated stem of pulmonary artery and of aortic arch with the aortic orifice of ductus arteriosus occluded by a thrombus (Fig 1 *A*)

measured 6 cm in circumference and had thin cusps, the wall of the left ventricle was 12 mm in thickness. The aortic ring was 5 cm in circumference, the leaflets were thin. The bulb and the arch of the aorta had a smooth, pale yellow surface. The aorta varied in its circumference, measuring 28 cm proximal to the ductus arteriosus, 31 cm at the orifice, and 28 cm in its descending portion. A sagittal section through the thrombus filling the pulmonary artery and the ductus arteriosus (Figs 3 and 4) showed an irregular thickness of the wall of the pulmonary artery. The dilatation of the vessel was conspicuous and brought about an invagination of the pulmonary orifice of the



Fig 3—Sagittal section through thrombus occluding pulmonary bulb and ductus arteriosus, the section is prolonged into the right ventricle and exposes the intact pulmonary valve

ductus arteriosus into the artery. The thrombus could be easily differentiated from the reddened wall of the pulmonary artery in all but three points, namely, at the juncture of the vessel with the ductus arteriosus and in two zones on the anterior wall of the pulmonary artery. In these foci the white vessel wall merged gradually into the gray thrombus.

Both lungs were quite voluminous and contained numerous dark blue, elevated, firm areas with a sharp but irregular outline separated from each other by pink crepitant lung tissue. On section these areas were irregularly wedge shaped, homogeneous, dark brown, and histologically showed the typical picture of an infected infarct.

The microscopic examination was confined to the pulmonary artery and to the ductus arteriosus and was greatly facilitated by drawings (the accompanying illustrations). By sagittal sections, a block was obtained which included in a cross section the stem of the pulmonary artery, the ductus arteriosus, and the thrombus (Fig 4). The wall of the pulmonary artery showed an unequal involvement. In some places a diffuse cellular infiltration with mononuclear and polymorphonuclear leukocytes was noted in all the layers, extending into the perivascular tissue. The surface was generally necrotic and covered with a thrombus. These processes were particularly conspicuous at several places of the anterior wall (Fig 5, *A*) but also were encountered in the posterior wall near the ductus arteriosus. In other places the infiltration was restricted to the intima and adjacent portions of the media. At the pulmonary orifice of the ductus arteriosus the infiltration of the whole wall was marked, diminishing

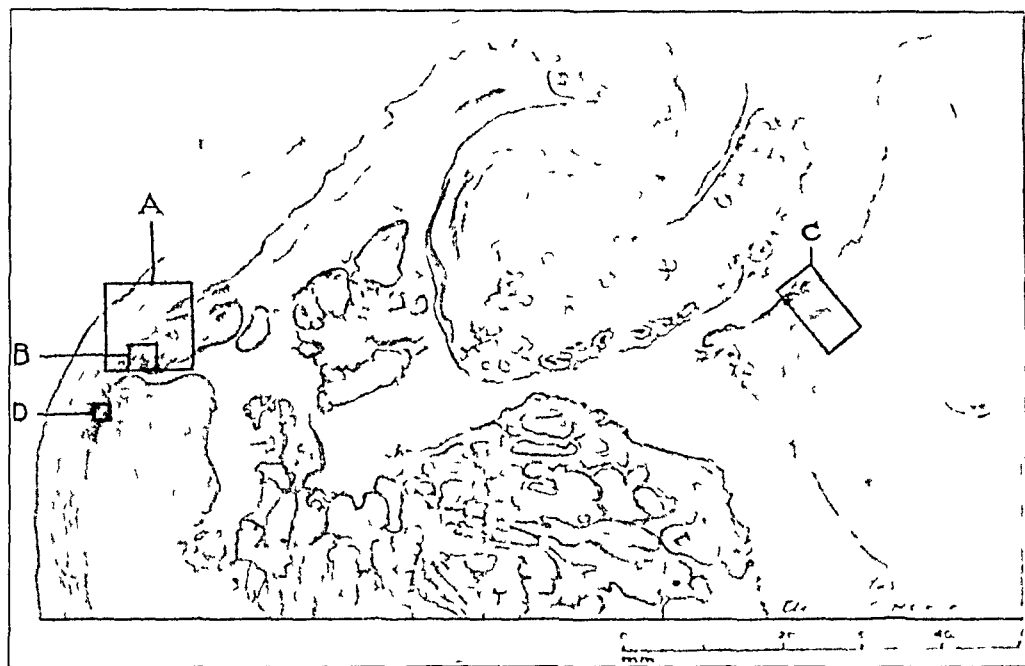


Fig 4—Side view of sagittal section through upper part of stem of pulmonary artery and ductus arteriosus. Squares indicate places from which areas of interest are taken and reproduced under higher power (Fig 5).

gradually in the upper aspect of the wall of the duct, whereas in the lower part it stopped rather suddenly (Fig 5 *C*). In the portion toward the aorta, the wall of the duct assumed a normal appearance. A moderate infiltration with mononuclear cells was present only in the loose perivascular tissue. At several places of the anterior wall in the pulmonary artery the thrombus had a warty appearance (Fig 5 *A* and *B*) and presented the same histologic structure encountered in infectious, valvular lesions of the heart. Organization of the thrombus was encountered in several places, notably at the pulmonary orifice of the ductus arteriosus and on the anterior wall of the pulmonary artery (Fig 5 *D*). A Gram stain of the section for bacteria was negative.

The case may be summarized. A boy, aged 8 years, who had always been well, came under observation through the school nurse for a "weak heart." The diagnosis of a patent ductus arteriosus was made. No untoward symptoms

developed until eight weeks before death when the child contracted a "cold" This was complicated by suppurative otitis media and joint pains which confined the child to bed and caused his admission to the hospital. Dyspnea was the dominant clinical feature, the heart was slightly enlarged toward the left at the apex, a soft systolic and a faint diastolic murmur were heard over the whole precordium. *Streptococcus viridans* septicemia was evident through repeated blood cultures. Necropsy confirmed the diagnosis of patent ductus

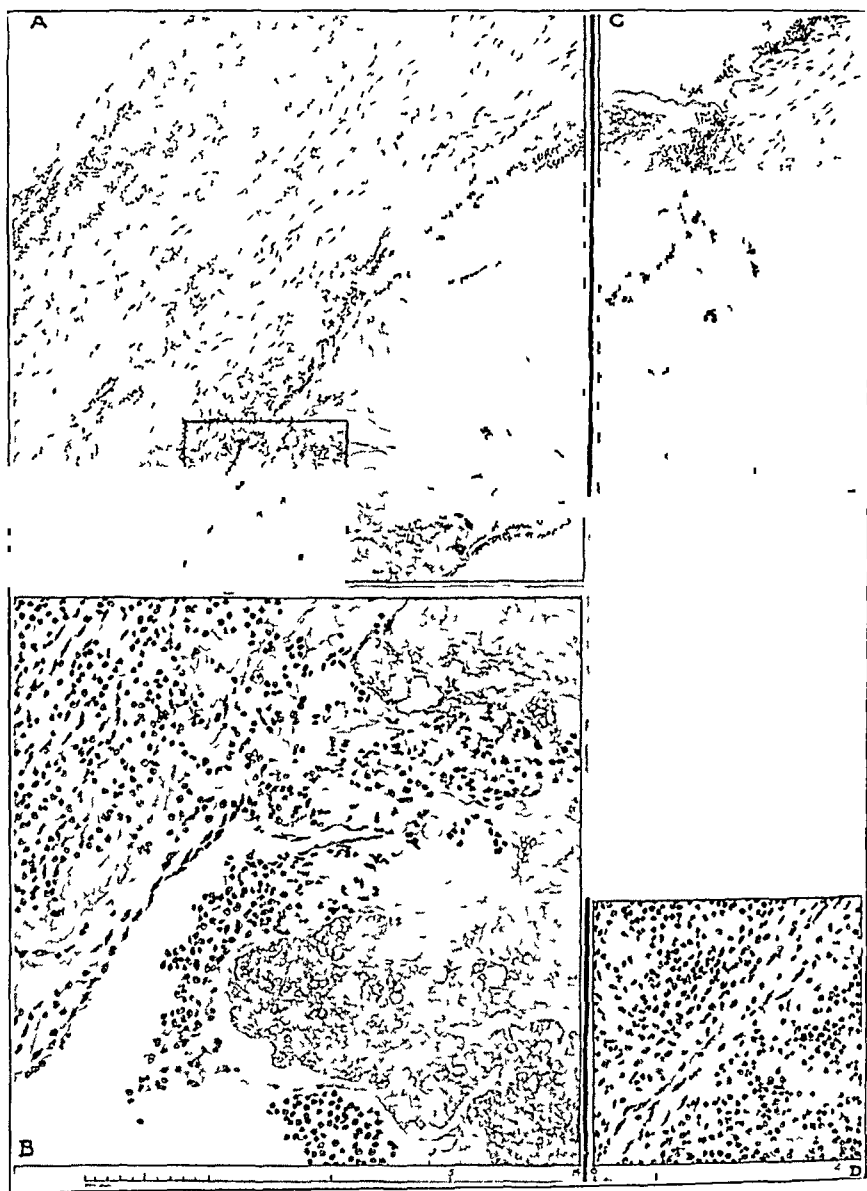


Fig 5—A, cellular infiltration involving all layers of wall of pulmonary artery, B, warty thrombus attached to inside of vessel wall, C, area of cellular infiltration at lower angle of pulmonary orifice of duct forming distinct wall of demarcation, D, zone taken from anterior wall of pulmonary artery where the thrombus is in process of organization

arteriosus. Although the heart valves were normal, there was an extensive arteritis of the pulmonary bulb with thrombotic occlusion and distention of the stem and main branches of the pulmonary artery, including the patent ductus arteriosus.

REVIEW OF CASES

Of the nineteen cases on record, six occurred in males and thirteen in females. Table 1 shows the distribution among the different decades of life.

TABLE 1—*Distribution of Cases in Decades of Life*

Decades	Number of Cases
1-10	1
11-20	4
21-30	9
31-40	4
41-50	1

Clinical data from the cases in the literature are entirely lacking in six instances and unequally detailed in the others. In a few instances only, the patient had subjective symptoms from his congenital heart lesion. In Sachs' ⁵ case and Babington's ⁶ case, palpitation was present from early childhood. Babington's patient (a woman, aged 34) had edema of the legs which subsided with rest. In the observations of Boldero ⁷ and of Murray, ⁸ the patients had been delicate all their lives and were not capable of ordinary work. Prior to the last illness cyanosis was noticed in one instance. A chronic cough in Buchwald's ⁹ patient was explained by the chronic pulmonary tuberculosis. Sommer's ¹² patient had four labors. In our case the parents of the boy did not suspect heart disease and the boy thought himself in perfect health.

Rheumatic fever is mentioned in the past history of four cases (Murray, ⁸ Hochhaus, ¹⁰ Weinberger, ¹¹ Boldero ⁷). Repeated attacks of sore throat were a feature of Sommer's ¹² case. In our case a double otitis media was noted shortly before the onset of the terminal illness. In reviewing the clinical findings of the heart, dilatation toward the left at the apex was noted in ten cases. In Rickards' ¹³ case the apex beat was felt in the sixth intercostal space. Dilatation toward the left

5 Sachs, R. Zur Kasuistik der Gefässerkrankungen, *Deutsch med Wchnschr* **18** 446, 1892.

6 Babington. *London M Gaz*, May, 1847, *Arch gen de med* **17** 214, 1847.

7 Boldero, H. E. A., and Bedford, D. E. Infective Endocarditis in Congenital Heart Disease Involving the Pulmonary Artery, *Lancet* **2** 749 (Oct 11) 1924.

8 Murray, H. M. Two Cases of Malformation of the Heart, *Tr Path Soc London* **39** 67, 1888.

9 Buchwald. Aneurysma des Stammes der Arteria pulmonalis. *Deutsch med Wchnschr* **4** 1, 13, 25, 1878.

10 Hochhaus, H. Beiträge zur Pathologie des Herzens, *Deutsches Arch f klin Med* **51** 1, 1893.

11 Weinberger, M. Ueber periphere Verengerung der Pulmonalarterie und das klinische Zeichen derselben, *Wien klin Wchnschr* **42** 1149, 1903.

12 Sommer, H. Ulceröse Endocarditis mit Mitbeteiligung des offenen Ductus Botalli, *Frankfurt Ztschr f Path* **5** 103, 1910.

13 Rickards, E. A Case of Ulcerative Endocarditis, *Brit M J* **1** 640, 1889.

at the base was recorded in four, dulness in the first and in the second intercostal space at the left of the sternum is reported in the cases of Hochhaus and Hamilton-Abbott. This dulness, known as the sign of Gerhardt and due to the dilatation of the pulmonary artery, was generally confirmed by the roentgenograms through the appearance of a bottle-neck shaped shadow in the pulmonic area, which in several instances showed marked pulsation on fluoroscopic examination¹⁴

In Buchwald's case, pulsation was visible not only over the apex but also in the second left intercostal space, it was wavy in character, disappearing on deep inspiration. Boldero noted a diffuse pulsation with the maximum in the second intercostal space.

In three instances (Buchwald, Hamilton, Boldero) a systolic thrill was palpable from the first to the third left intercostal space, the maximum being in the second space.

The murmur caused by the patent ductus arteriosus at the pulmonic area was loud, systolic in time, and extended into the diastole with accentuation of the second pulmonic sound. It was noted in the cases of Buchwald,⁹ Foulis,¹⁵ Rickards,¹³ Murray,⁶ Hochhaus,¹⁰ Weinberger,¹¹ Sommer,¹² Hamilton,² Boldero,⁷ and in our case. Rickards and Foulis described it as a double murmur. In our case a soft systolic and a faint diastolic murmur was heard over the whole precordium. The murmur was transmitted upward into the left carotid and the left subclavian artery. According to Frank, it was not transmitted to the back. Boldero, however, states that in his case the murmur was harsh and continuous also in the back of the chest. In the case of Boldero (a man, aged 29) the blood pressure was 200 systolic, 90 diastolic. The Wassermann reaction, recorded in our observation only, was negative.

The duration of the terminal illness with fatal outcome varied between two months (Buchwald, Hamilton) and two years in Boldero's case. The course was always progressive, the picture was that of an acute or subacute blood stream infection with intermittent fever accompanied with heart symptoms of variable degree. Death occurred from cardiac failure. The blood culture revealed *Streptococcus viridans* in Terplan's¹⁶ and in our case, Hochhaus¹⁰ recovered *Staphylococcus albus*, Schlagenhauser,¹⁷ influenza bacilli, and Hamilton and Abbott,² pneumococci.

14 Wessler and Bass, cited by Hamilton and Abbott (Footnote 2)

15 Foulis, J. On a Case of Patent Ductus Arteriosus with Aneurysm of the Pulmonary Artery, Edinburgh M. J. **30** 17, 1884

16 Terplan, K. Mykotisches Aneurysma des Stammes der Pulmonalarterie mit Endocarditis des offenen Ductus Botalli bei einem Falle von Endocarditis lenta, Med. Klin. **20** 1331, 1924

17 Schlagenhauser, F. Ein Fall von Influenza-endocarditis der Aortenklappen und des offenen Ductus Botalli, Ztschr. f. Heilk. **22** 19, 1901

ANALYSIS OF NECROPSY FINDINGS

In the observation of Terplan and of Kizyszkowski, an exudate was present in the pericardial sac, serofibrinous in one and hemorrhagic in the other

Dilatation and hypertrophy of the heart were mentioned in almost all instances, hypertrophy involving both sides, dilatation being restricted to the right heart. The thickness of the right heart muscle varied between 0.3 cm in our 8 year old boy and 1 cm in Sommer's 45 year old woman. Boldero's⁷ 29 year old man also had a heart wall 1 cm in thickness.

Examination of the mitral valve revealed fresh vegetations in five instances (Babington, Buchwald, Foulis, Murray, Hochhaus). Weinberger¹¹ reported a chronic lesion of the ring and three authors (Sachs,⁵ Hart,¹⁸ Case 2, Sommer¹²) mentioned merely a thickening of the cusps, pointing to a healed process.

The aortic valve was damaged in thirteen out of the nineteen cases. The nine observations in which the mitral orifice was inflamed also showed a lesion of the aortic valve. The aortic vegetations were the only lesion in the left heart in the cases of Kidd,¹⁰ Schlagenhauser,¹⁷ Hart,¹⁸ Case 1, Terplan,¹⁶ and Boldero.⁷ In all instances the lesions were acute except in Babington's⁶ patient (a woman, aged 34) in whom the ring was stenosed by calcified vegetations.

The tricuspid valve was bordered by fresh vegetations in Murray's⁸ case with similar lesions on the mitral and the aortic valve. Vegetations on the pulmonary valve were found in nine cases. In all instances the stem of the pulmonary artery and the patent ductus arteriosus were the seat of an arteritis with thrombus formation. In the remaining ten cases the pulmonary valve was normal but the pulmonary artery and the ductus arteriosus showed a more or less extensive inflammation. Three cases of this second group, including ours, are unusual as far as the arteritis was not complicated by any valvular endocarditis.

The points of interest are the extent and the character of the lesions in the pulmonary artery with the possible dilatation resulting from the chronic inflammation and the changes observed in the ductus arteriosus. We shall first review the findings in the pulmonary artery of the cases with a pulmonary or other valvular lesion, then analyze separately the observations of the three cases without any complicating endocarditis. Finally, the anatomic findings in the patent ductus arteriosus will be

18 Hart, C. *Ulcerose Endocarditis mit Mitbeteiligung des offenen Ductus Botalli*, Virchows Arch f path Anat **177** 218, 1904

19 Kidd, Percy. *Embolie Aneurysm of Pulmonary Artery, Infective Aortic Valvulitis, Aortitis and Pulmonary Endocarditis, Patent Ductus Arteriosus*, Tr Path Soc, London **44** 47, 1893

TABLE 2—*Summary of Cases*

Author and Year of Publication	Sex* and Age	Clinical Data,†	Condition of Heart Valves‡	Condition of Pulmonary Artery	Form and Condition of Ductus Arteriosus	Bacteriology ?	Remarks
Babington 1847	♂ 34	P H Palpitation since childhood, no rheumatism	M Fresh vegetations A Vegetations in part calcified	Fusiform dilatation of stem	Funnel shape, widely patent small vegetations at pulmonary orifice	?	Infarcts of lungs
Buchwald 1878	♀ 21	P H Chronic cough, pulmonary tuberculosis	P Numerous vegetations M Fresh vegetations A Fresh vegetations on leaflets	Triangular area on interior wall from valve to duct occupied by thrombus	Funnel shape, vegetations on both openings	?	Forked embolus in branch of lower left lobe of lung
Fouls 1884	♀ 22	P H Scarlet fever at 16, no rheumatic fever	M Verrucose vegetations A Full of vegetations	Thrombi on left side of wall partly filling great aneurysm covering left auricular appendage	Funnel shape pulmonary orifice occupied by thrombus	?	Infected thrombi in branches of pulmonary artery
Murray 1888	♀ 36	P H Always delicate, rheumatic fever at 26 P I Malignant endocarditis	T Vegetations on free border M Vegetations A Vegetations	Anterior wall up to duct covered with thrombus	Funnel shape, thrombus at pulmonary orifice, aortic mouth, shows calcium deposit	?	Infarcts of spleen and kidney
Richards 1889	♂ 17	P H Always thin and pale	P Polypoid vegetations	Partially occluded by thrombus up to pulmonary orifice of duct	Vegetations around pulmonary orifice	Micrococci	Infarcts of lungs and kidneys, vegetations on aortic wall opposite duct
Stubs 1892	♀ 21	P H Palpitation since childhood P I Malignant endocarditis	P Verrucose vegetations M Slightly thickened A Extensive vegetations	Longitudinal rows of thrombi on anterior wall throughout whole length	Funnel shape thrombus occluding pulmonary orifice	?	Infarcts of lung and spleen, aneurysm with thrombi in branches of pulmonary artery amyloid degeneration of spleen, liver, kidney, intestine
Hochhaus 1893	♂ 24	P H Rheumatic fever at age of 12 P I Recurrent mitral endocarditis	P Vegetations M Vegetations A Vegetations	Small cauliflower like vegetations up to duct	Funnel shape, vegetations around pulmonary orifice	Staphylococcus albus	Infarcts of lung and spleen vegetations opposite orifice of ductus arteriosus
Kidd 1893	♀ 22	P I Dyspnea	P Healthy A Large soft vegetations	Crop of warty fibrous vegetations on posterior wall	Fibrous vegetations on aortic orifice	?	Aneurysm of branch of left pulmonary artery surrounded by healthy lung tissue, in aorta sacular aneurysm near duct
Gauchery 1900	♀ 27	No data	P Vegetations	Thrombus from valve to duct, fusiform dilatation of stem	Vegetations forming fringe around pulmonary orifice and in duct	?	Multiple septic emboli, organs not mentioned
Schlagenhauer 1901	♂ 13	P I Subacute bacterial endocarditis	A Vegetations	Numerous vegetations in whole bulb	Both orifices and duct covered with vegetations	Influenza bacilli	Multiple infarcts of lungs
Krzyszowski 1902	♀ 17	P I Hemoptysis	Normal	Fusiform dilatation thrombus adherent to anterior wall	Funnel shape pulmonary orifice occupied by thrombus	?	Infarcts of lungs aneurysms of smaller branches of pulmonary artery

TABLE 2—Summary of Cases—(Continued)

Weinberger	Q	P H	Rheumatic fever	P	Numerous vegetations	Scattered thrombi on anterior wall	Aortic orifice and duct lined with vegetations	?
1903	37							
Hart (I)	♂ 23	P I Anemia intermittent fever		M A	Chronic lesion No vegetations Red vegetations	Vegetations forming lines from duct to valve	Funnel shape, duct and pulmonary orifice covered with small vegetations	?
Hart (II)	♀ 24	P I Anemia		M A	Thickening Cauliflower, pink vegetations in sinus of Valsalva	Beddled with small vegetations extending into branches of pulmonary artery	Duct filled with pinpoint vegetations	° Not determined
Sommer	♀ 15	P H Repeated angina P I Dyspnea and edema of legs for 9 months		P M	Vegetations on anterior leaflet Thickened, no fresh vegetations	Numerous thrombi from duct to valve	Tunnel shape, pulmonary orifice narrowed by vegetations	?
Hamilton and Abbott	♀ 19	P H Pale and slender P I Symptoms of general infection for 2 months		A	Ulcerative vegetations Normal	Thrombus on interior wall extending into left branch (pulmonary bulb dilated)	Vegetations around pulmonary orifice and adjacent part of duct	Pneumococci
Wycliff	♀ 35	P I Arthritis of spine		M A	Chronic Large ulcerative vegetations	Thrombus on anterior wall throughout whole length (pulmonary bulb dilated)	Both openings filled with vegetations	Streptococcus viridans
Boldero and Bedford	♂ 29	P H Always delicate, rheumatic fever in childhood, diptheria at 7		P A	Extensive vegetations Covered with vegetations Normal	Numerous wiry vegetations on anterior wall throughout whole length	Duct filled with small watery vegetations	?
Sehler	♂ 8	P H No rheumatism P I Double otitis media				Fusiform dilatation of stem on interior and right side, adherent thrombus filling lumen	Thrombus adherent to pulmonary orifice filled duct	Streptococcus viridans
Rauchfuss, C	♂ 8 days	Omphalitis, septicæmia					Pituitary ductus occluded by partly puriform, softened thrombus	No emboli mentioned
Rauchfuss, C	♀ 10 days	At 8 days, erysipelas starting at umbilicus and spreading					Duct 15 mm long filled with thrombi protruding through pulmonary orifice into pulmonary artery not protruding into aorta	Infarcts of lungs, peritestinal hemorrhages in intestines, pus in joints, infected thrombi in umbilical vessels
Rauchfuss, C	♀ 16 days	Omphalitis, arthritis, cerebrospinal meningitis					Duct 17 mm long and 5 mm in diameter partly filled by softened thrombus, not protruding into aorta	No emboli mentioned
Rauchfuss, C	♀ 19 days	Enteritis				From duct, extending into right branch	Funnel shape, filled by thrombus protruding into aorta	Emboli in lungs and kidneys, infection of umbilical cord not demonstrated

* In this table, ♂ indicates male, ♀, female

† P H, past history, P I, present illness

‡ T, tricuspid, P, pulmonary, M, mitral, A, aortic

summarized and the nature and the extent of the inflammatory lesion in this anomaly of the heart reviewed

In the cases with a pulmonary or other valvular lesion the arteritis in the pulmonary artery was always accompanied with thrombosis. The thrombus generally involved the anterior wall of the artery. In Foulis' case the thrombus was more adherent to the left side of the stem of the pulmonary artery. Kidd found a crop of warty vegetations attached to the posterior side of the pulmonary artery. He is the only author who does not stress the fact that the anterior and the upper walls of the stem of the pulmonary artery were the seats of inflammation. In all instances the vegetations were described as soft and polypoid. Boldero noted that in his case the thrombus completely occupied the lumen of the vessel. In Buchwald's observation, there was a triangular area of attachment of the thrombus with the base at the pulmonary valve and the apex at the ductus arteriosus. Rickards' patient also had a thrombus adherent to the anterior wall partly occluding the lumen of the pulmonary artery. Numerous small thrombi adherent to the wall of the pulmonary artery were reported by Hochhaus, Gauchery²⁰ and Sommer. Sachs and Foulis had lines of thrombi forming crests of irregular thicknesses from the valve to the ductus arteriosus. In Hart's first case the vegetations formed lines, in his second case stem and branches of the pulmonalis were riddled with pinpoint sized vegetations. Also Schlagenhauser and Weinberger found numerous small vegetations in the pulmonary artery. In Murray's case the thrombi formed an oval mass on the anterior and upper aspect of the dilated artery. In Terplan's case, the thrombus occupied a large part of the pulmonary artery.

The following three cases are reviewed separately because the pulmonary artery with the patent ductus arteriosus were the only seats of inflammation. In Krzyszkowski's case, 2.5 cm above the valve the anterior wall of the pulmonary artery and its left main branch were occluded by a thrombus. Hamilton and Abbott found the pulmonary artery occupied by a large, moist gray thrombus attached to the anterior and upper wall. Pyramidal in shape, the thrombus had its broad base vertically in the lumen of the pulmonary artery, leaving the right half of the stem and the right main branch free. The central end of the thrombus was situated 1 cm from the pulmonary valve. With its upper end, the mouth of the ductus arteriosus was plugged. In our case the pulmonary artery and both main branches were filled by a gray-white and red thrombus. It was adherent to the wall except in the posterior left aspect of the pulmonary bulb.

20 Gauchery, F. Persistenz des Ductus Botalli, Endocarditis ulcerosa der Arteria pulmonalis und aneurysmatische Erweiterung des Anfangsteiles d. Pulmonalis, *Centralbl f allg Pathol u path Anat* 2: 70, 1900

The chronic infection of the arterial wall produced in many instances of arteritis of the pulmonary artery a fusiform dilatation at the site of greatest damage. Terplan mentioned a dilatation in the area of attachment of the thrombus to the vessel wall. Krzyszkowski and Hamilton noted a fusiform dilatation of the pulmonary bulb, also observed in our case. Foulis reported a dilatation to the left with the result that the aneurysm covered the left auricular appendage.

The anatomic findings in the duct may be summarized. In eight instances the patent ductus arteriosus had a funnel shape with a narrowing of its pulmonary orifice. In others, as in ours, the canal had about the same caliber throughout. The length and the width of the duct varied. Boldero mentioned 1.5 cm. as the length in his 29 year old man, Hamilton-Abbott, 7.5 mm. (a woman, aged 19). In our patient (a boy, aged 8) the duct measured 7.5 mm. Hochhaus' figure is 6 mm. (a man, aged 24), Schlagenhauser gives 5 mm. (a boy, aged 13 years), Sachs, 3 mm. (a woman, aged 21). Babington called the duct in his 34 year old woman, widely patent. Foulis and Murray could pass a goose quill, Sachs measured 3 mm. width, Schlagenhauser, 4 mm., we found 2.5 mm.

The extent of the arteritis in the ductus arteriosus varied in the different observations. In eleven of the nineteen cases, the pulmonary orifice alone was the seat of thrombi filling the duct in part (Hamilton) or completely (Schlaepfer) without any evidence of attachment to the wall except at the pulmonary orifice. Also in Krzyszkowski's observation, the pulmonary orifice was the only affected part. Microscopically, in our case, the wall was involved for only a short distance at the pulmonary mouth, whereas in Hamilton's case the wall was inflamed in its whole length. Hamilton mentioned a calcified lymph node which was adherent to the outside of the wall. In three instances (Buchwald, Kidd, Terplan) both orifices of the duct were fringed with vegetations, no notes were found about the condition of the duct itself. In five cases (Schlagenhauser, Hart, Cases 1 and 2, Weinberger, Boldero) small, warty vegetations narrowed the lumen of the duct.

Some findings of note deal with changes in the aorta in the vicinity of the opening of the duct. In Foulis' case, a saccular aneurysm with atheromatous changes was found opposite the mouth of the duct. An analogous observation was noted by Hochhaus. The inside of the sac was filled with small thrombi which were adherent to the wall. Rickards noticed similar adherent thrombi in the same location without any aneurysm formation. This part of the aorta was attached to the trachea. Babington mentioned atheromatous changes in the aorta opposite the duct.

A fold arising from the aortic wall central to the opening of the duct, protruding into the lumen of the aorta, was noted by Babington, Buchwald and Hochhaus. Babington mentioned in addition a narrowing of the descending portion of the aorta. Hamilton in his case also found a narrowing of the descending aorta (coarctation). Our patient showed a slight dilatation of the aorta beyond the aortic orifice of the duct, further down the aorta was normal.

The necropsy findings in the other organs of the nineteen cases are of interest as they were the result of thrombi broken off from a valve, the pulmonary artery, or the patent duct. As infected thrombi, they produced infarcts and inflammation in the lungs, the spleen, the kidneys, the intestines, the skin and the brain. The lungs were the seat of multiple infarcts in thirteen cases. In some instances the process had progressed to abscess formation. A rather peculiar feature was the formation of saccular aneurysms in the smaller branches of the pulmonary artery (Sachs, Kidd, Krzyszkowski). In nine cases infarcts of the spleen were mentioned, of the kidneys in seven.

COMMENT

In instances of arteritis of the pulmonary artery associated with patent ductus arteriosus, the clinical symptoms and signs of a patent duct persist but may become complicated and masked by the infectious process and occlusion of the duct by a thrombus. The signs of a patent duct may be summarized as follows: (1) dulness in the first and in the second left intercostal space next to the sternum (Gerhardt), (2) enlarged pulmonary artery in the form of a bottle neck shaped shadow in the roentgenogram, (3) pulsation in the area of dilatation on fluoroscopic examination, (4) enlarged cardiac dulness at the apex associated with ventricular dilatation and hypertrophy, (5) visible pulsation at the apex especially on deep expiration, or a palpable thrill over the apex which is also felt in the second left intercostal space and at the jugular notch, (6) a loud systolic murmur extending into the diastole with accentuation of the second pulmonary sound, best heard in the pulmonic area, but transmitted from there to the neck and to the left arm but generally not into the back. The signs of a superimposed arteritis can only be assumed from the presence of the well known signs of a subacute bacterial endocarditis. The infarcts in various organs, such as the lung, the spleen and the kidneys, and in the skin may help to make an accurate diagnosis.

The pathology of the cases reviewed in this article shows that dilatation and hypertrophy of the heart results and is particularly marked in the right side. This is the mechanism whereby the difference in pressure in the aorta and in the pulmonary artery is brought to an equilibrium.

The normal ratio of the pressure in the aorta and in the pulmonary artery is 5 2 according to Goltz-Gaule, and 3 1 according to Marey. The difference in pressure is met by the muscular hypertrophy of the right side. The diameter of the lumen of the patent ductus arteriosus is a determining factor for the blood flow.

In sixteen out of nineteen cases, some valvular lesions of the heart were present. In these cases and in the three others put together in a special group, the pulmonary artery and the ductus arteriosus were the seat of a chronic arteritis. It may be interesting to note the interpretation given by previous observers of such lesions and see how they correlated the different findings. The explanation will vary somewhat according to the group of lesions present in a given personal observation.

Mechanical injury to the wall of the pulmonary artery by the constant blood flow from the aorta through the ductus arteriosus was, according to Foulis, the main factor for the formation of an aneurysm in his case. Foulis did not stress the presence of infection in the arterial wall. Weigert-Sachs first emphasized the predisposition of circumscribed portions of the pulmonary artery to arteritis by the mechanical traumatism of an abnormal blood flow from the aorta through the patent duct. Sommer also took up this explanation for the localization of the thrombo-arteritis on the anterior wall of the pulmonary bulb in the prolongation of the long axis of the duct. Hamilton and Abbott mentioned the possibility of infected emboli in the vasa vasorum of the affected portion of the pulmonary artery. In minute tears of the intima resulting from mechanical strain, an infection with subsequent thrombosis may start through circulating micro-organisms.

Generally the way of infection is assumed to take place by a blood flow from the aorta through the duct into the pulmonary artery. Buchwald and Weinberger assumed in their case first a lesion of the pulmonary valve and from there a propagation into the pulmonary artery. This argument holds true for only a group of cases.

The fusiform dilatation of the pulmonary artery observed in many of these cases is the result of the weakening of the wall in the presence of a chronic infection. Posselt,²¹ however, showed that in many cases of patent ductus arteriosus without any complicating arteritis a dilatation of the pulmonary artery is frequently encountered.

The funnel shape of the ductus arteriosus at its aortic orifice may partly be explained by the relative absence of elastic fibers in the media, as demonstrated by Busse.²² On the same basis Busse explains the

21 Posselt. Die Erkrankungen der Lungenschlagader, Lubarsch-Ostertag, *Ergebn d allg Pathol u path Anat* **13** 352, 1909.

22 Busse, O. Zur normalen und pathologischen Anatomie des Ductus Botalli, *Cor-BI f schweiz Aerzte* **48** 457, 1918.

frequency of atheromatous changes in this location. In a review of cases of patent duct Rokitsky²³ found the duct funnel shaped in most instances, in only a few cases was the duct short with a uniform, large lumen throughout. In all cases Rokitsky observed a dilatation and hypertrophy of the right ventricle. Some hypertrophy also was present in the left heart. Repeatedly he noticed a narrowing in the descending portion of the aorta, as encountered by Hamilton and Abbott.

The four cases of Rauchfuss with thrombosis of the arterial duct in new-born infants are unique and stimulate a more careful examination of the duct when necropsies are being performed on babies.

SUMMARY

Chronic and acute arteritis of the pulmonary artery and of the patent ductus arteriosus has been observed in nineteen cases. To two of these cases in which no additional valvular lesions were found, a third is added.

In all nineteen cases, the picture was that of a subacute bacterial endocarditis with the signs of a patent ductus arteriosus.

The seat of the arteritis is undetermined. Satisfactory evidence is not at hand to determine the influence of the force of the blood flow passing from the aorta through the duct into the pulmonary artery. The anterior wall of the pulmonary artery and the pulmonary orifice of the duct are the places of predilection.

Dilatation of the stem of the pulmonary artery is often accompanied with a patent ductus arteriosus, in cases of arteritis, an aneurysmal bulging results at the site of the thrombus on the vessel wall.

Narrowing (coarctation) of the descending aorta is an anomaly frequently associated with patent ductus arteriosus. It facilitates the blood flow through the duct and thereby increases the traumatism to a circumscribed part of the anterior wall of the pulmonary artery.

123 Grand Avenue

²³ Rokitsky, C. Ueber Persistenz des Ductus arteriosus, Ztschr f d Gesellsch d Aerzte in Wien 1 137, 1864

THE POSSIBLE RELATIONSHIP BETWEEN ACROMEGALY AND DIABETES

WITH REPORT OF THREE CASES *

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According to the figures given by various authors, diabetes occurs in from 10 to 40 per cent of the cases of acromegaly. Even the lowest of these figures is sufficiently high to suggest that this is more than a coincidence, that there must be some common factor underlying both conditions. In going over the older literature one finds that most of the diagnoses of diabetes in these cases have been made on the basis of the urinary examinations for sugar. In considering this subject, therefore, we must bear this point in mind for in the light of more recent work we know that glycosuria is not always a true indication of diabetes.

In an analysis of all cases of pituitary disease which have been seen at the Cleveland Clinic, comprising forty-one cases to date, seven cases of acromegaly were found, diabetes being present in two of these, 28.5 per cent. Were we to consider pituitary tumor as a causative factor in the production of diabetes, then we might suppose that the opposite clinical entity, namely, hypopituitary disease, would be marked by an increased carbohydrate tolerance. Of the forty-one cases of hypopituitary disease referred to above, there was no glycosuria in twenty-six, and in five there was more or less marked diabetes, thus, 16 per cent of this group showed a decreased carbohydrate tolerance. If acromegaly, which is due to hyperpituitarism, produces diabetes, on the other hand the reverse condition, hypopituitarism, certainly does not offer any protection against diabetes.

Diabetes in cases in which either hyperpituitarism or hypopituitarism also is present does not differ from diabetes in cases in which these disturbances of pituitary function are not present. Moreover, the removal of the pituitary gland certainly does not cure a case of diabetes, and no authentic case of cure by such means has ever been reported in the literature. That the secretion of the pars posterior and the pars intermedia has something to do with carbohydrate metabolism is shown by the fact, as has been reported in the literature, that injection of pituitary extract (pars posterior) causes hyperglycemia and glycosuria. It would appear, therefore, that hypertrophy of the gland ought in part to have the same effect as injection of the extract, although the effect

* From the Cleveland Clinic

of the former should depend largely on the functional activity of the posterior and possibly of the intermediate lobes rather than on the size of the tumor

Against the hypothesis that the pituitary gland is the sole factor in disturbances of carbohydrate metabolism may be cited the fact that removal of the pituitary tumor does not cure diabetes. It may improve the condition, as some observations seem to indicate, but the data are not conclusive, as in the literature glycosuria is not fully differentiated from true diabetes. Moreover, in cases in which the patients are reported to have improved or recovered after removal of the pituitary gland, it may be that the diabetes had merely been held in check by strict adherence to the appropriate diet. Just such a status is frequently seen in cases of diabetes in which a marked hyperglycemia is present when the patients are on a moderate diet, but if the condition has been brought under control they can take a much higher diet without any increase in the blood sugar beyond the normal range. Whether this changed status is due to a functional improvement of the insulogenic function or to regeneration of the islands of Langerhans is not known.

The following two cases, in each of which diabetes developed years after the acromegaly was recognized, illustrate the fact that diabetes associated with acromegaly does not differ materially, as far as we can observe, from diabetes without acromegaly, that the same treatment is applicable to the former as to the latter types of cases of diabetes, that in each the same results may be expected under proper treatment, and that in each case, if the patient is untreated or is improperly treated, the same increased loss of carbohydrate tolerance, acidosis and coma ensues.

REPORT OF CASES

CASE 1—A man, aged 55, came to the Cleveland Clinic in March, 1925, complaining of general weakness, intense thirst and polyuria. The patient had had none of the diseases of childhood but had had pneumonia and rheumatism in later life. At the age of 22 his head had been injured and his leg broken in an accident. In 1924 he had had some teeth extracted. Apart from his rheumatism, he had been fairly well until December, 1924, about three months before I saw him, when he had an attack of hiccups which lasted for five days, and glycosuria was discovered by his family physician, who had been treating him with insulin. At times he had double vision and his eyelids drooped a little. He had some dyspnea on exertion and his rectum frequently prolapsed. During the preceding three months he had lost 37 pounds (16.8 Kg.).

Physical examination disclosed a tall man, 6 feet, 1 inch (185.4 cm.) in height, weighing 203 pounds (92.1 Kg.), with coarse features and large joints and fingers of the acromegalic type (Figs 1 and 2). There was marked hypertrophic arthritis of the hands and roentgen-ray examination revealed Heberden's nodes on the fingers (Fig 3). The pulse rate was 104, blood pressure 105 systolic, 78 diastolic. The scalp was very thick and wrinkled, with protruding supraorbital ridges, the cheeks and jaw were very prominent.

The growth of the skull, the hands and the feet during the preceding ten years is shown by the following comparative measurements

	Hat	Glove	Shoe	Shirt
1915	7 $\frac{3}{8}$ "	No 10	No 9	16 5
1925	7 $\frac{5}{8}$ "	No 13	No 12	17 5

Roentgen-ray examination showed a large sella turcica (Fig 4)

Laboratory findings were as follows *Urine* sugar, 5 per cent, acetone, 4 plus, diacetic acid, plus, trace of albumin, few hyaline casts *Blood* red blood cells, 4,550,000, white blood cells, 5,900, hemoglobin, 85 per cent

In this case it was not necessary to make a glucose tolerance test in order to confirm the diagnosis of diabetes, as the presence of a 5 per cent glycosuria with a fasting blood sugar value of 440 mg per hundred cubic centimeters is sufficient evidence of the condition, but in view of the statements by his physician that neither insulin nor a month's treatment with pituitary extract had benefited him at all, the glucose tolerance test was made for final proof (Table 1 and Fig 5)

TABLE 1—*Glucose Tolerance Test on Day After Admission*

	Blood Sugar Before and After Ingestion of 100 Gm of Glucose in Mg per 100 Cc	Sugar in Urine in Gm
Before	440	3 plus
One half hour after	543	
One hour after	626	6 27
Two hours after	680	17 5
Three hours after	600	12 0
Four hours after	506	11 5
Total water intake, 860 cc	Total sugar intake, 100 Gm	
Total urine output, 1,010 cc	Total sugar output, 47 27 Gm	
Corpuscle volume at start, 36 per cent		Mg per 100 Cc
Plasma chlorids		530
Blood urea		51
Blood uric acid		2 7
Blood creatinin		1 6
Nonprotein nitrogen		55 6
Plasma acetone, trace		

It was evident that the prime need was to treat the diabetic condition. The patient was therefore placed in our diabetic hospital, on a diet of 100 Gm of carbohydrate, 60 Gm of protein, and 128 Gm of fat, a total of 1,800 calories, on which he gained 5 pounds (2 3 Kg) during the first twenty-four days, but later lost 10 pounds (4 5 Kg). He received an average of 100 units of insulin per day in four doses, 40, 20, 20 and 20 units, respectively, for ten days, at the end of which time his blood sugar had reached the normal level. He then received 20 units per day for about two weeks and only three doses after that. April 17, his diet was increased to 120 Gm of carbohydrate, 80 Gm of protein, 133 Gm of fat, a total of 2,000 calories, and the insulin was discontinued. As Figure 6 indicates he kept a normal blood sugar level until he was discharged, April 20. The twenty-four hour sugar output in the urine was as follows: March 25, 78 75 Gm; March 26, 27 00 Gm; March 27, 1 54 Gm; March 28-30, trace; after March 31, none.

A double iridectomy was performed on April 17, as he had developed acute cataracts in both eyes, one lens was removed a few days later. The cataracts had developed rapidly, for when the patient entered the clinic the lenses were clear, but within a few days a lenticular change began, the progress of which could be seen from day to day, a surprising circumstance, as one would expect that the control of the diabetic condition would prevent any further retrogressive eye changes. The visual fields could not be measured on account of the cataracts.

The report of Dr A D Ruedemann of the ophthalmologic department of the clinic was as follows

- 3/20/25 Vision right eye on entrance, 6/15, vision left eye on entrance, 6/20
Improved with a plus 2 lens to 6/10, tension (Schiotz) 25 in both eyes The examination revealed early lenticular changes in both eyes with no changes in the disk or retina
- 4/ 3/25 Heavy central opacities, vision reduced to 6/60, not improved with glasses No changes in the fundus Fields of vision could not be taken on account of the opacities in the lenses
- 4/17/25 Double iridectomy was performed, which did not materially improve the vision, so the right lens was extracted



Fig 1—Patient with acromegaly associated with diabetes, showing development of acromegalic features

The patient was seen by me again nearly three months later. During the interim, he had been living on a liberal diet, practically the only things he had eliminated were sugar and pastry. At this time, his fasting blood sugar was 105 mg per hundred cubic centimeters, and there was no glycosuria present. A glucose tolerance test was then made, which, to my astonishment, gave a normal curve, the first normal curve in a diabetic case that I have ever encountered (Fig 7). The clinical progress together with the fasting blood sugar level suggested a marked improvement, but the glucose tolerance test demonstrated that the functional capacity of the island tissue had been restored to normal. In other words, the diabetic condition had been cured. The question which remains unanswered is, Is this a permanent cure, or under some undue strain, will the pancreas again break down? This naturally cannot be answered at

this stage, but we hope to be able to follow this patient, if in a decade or two he still remains normal, this will be an authentic case of a permanent cure of diabetes

This is a typical case of the association of diabetes with acromegaly. Because of the acromegaly the diabetic status had not been recognized, the polyuria being considered to be due to the pituitary condition,

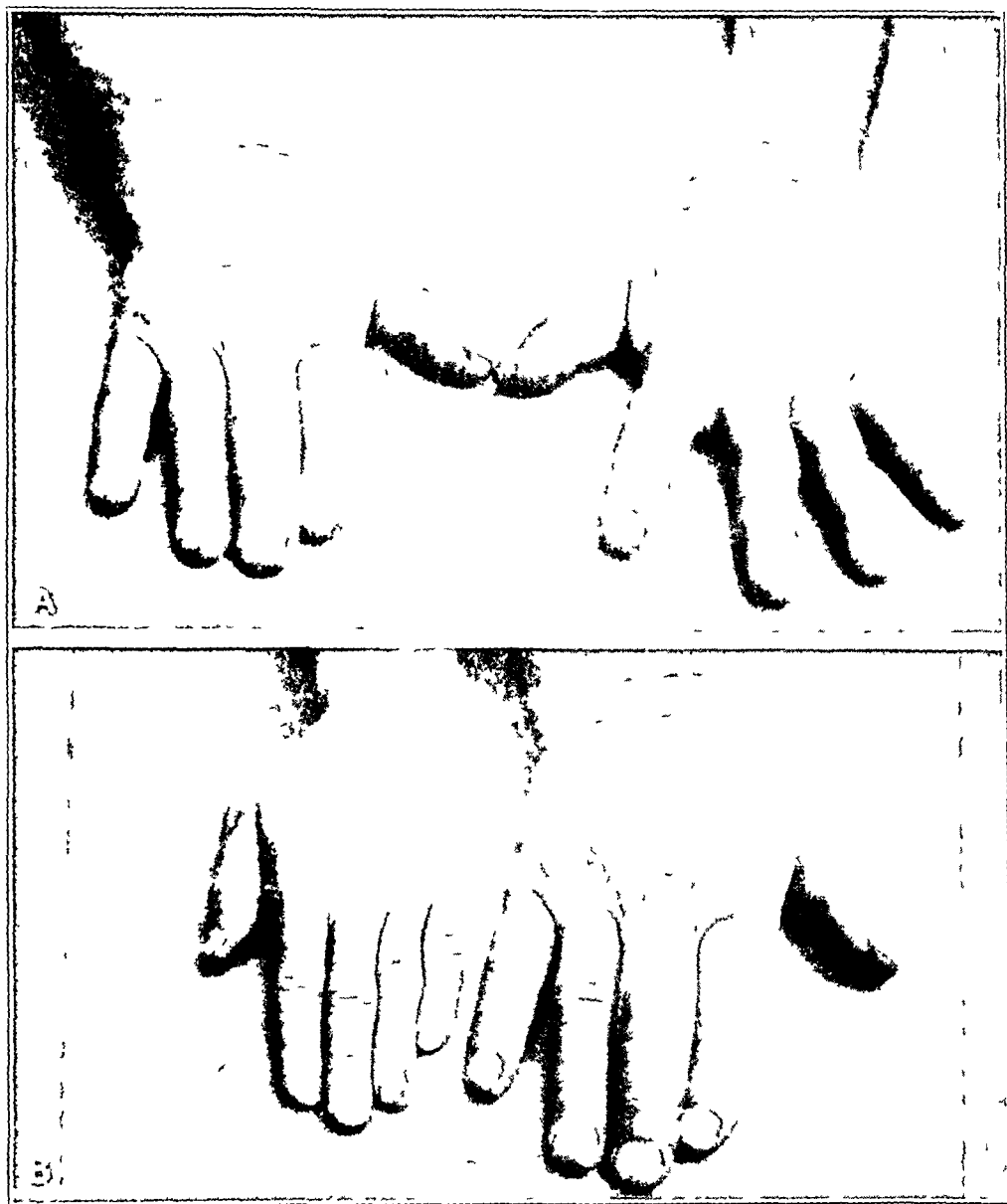


Fig 2—*A*, acromegalic hands of patient shown in Figure 1, *B*, acromegalic hand of same patient compared with normal hand

although pituitary extract did not improve the condition, which grew worse daily

In this patient the acromegaly preceded the diabetes by ten years. It does not seem probable that if acromegaly, or hyperfunction of the

hypophysis, causes diabetes, it could be present for ten years without exerting any apparent influence on the metabolism of carbohydrates and then suddenly produce diabetes. It would appear more probable that ten years after the initiation of the acromegaly, some other factor was introduced which produced the diabetes. Was it the rheumatism

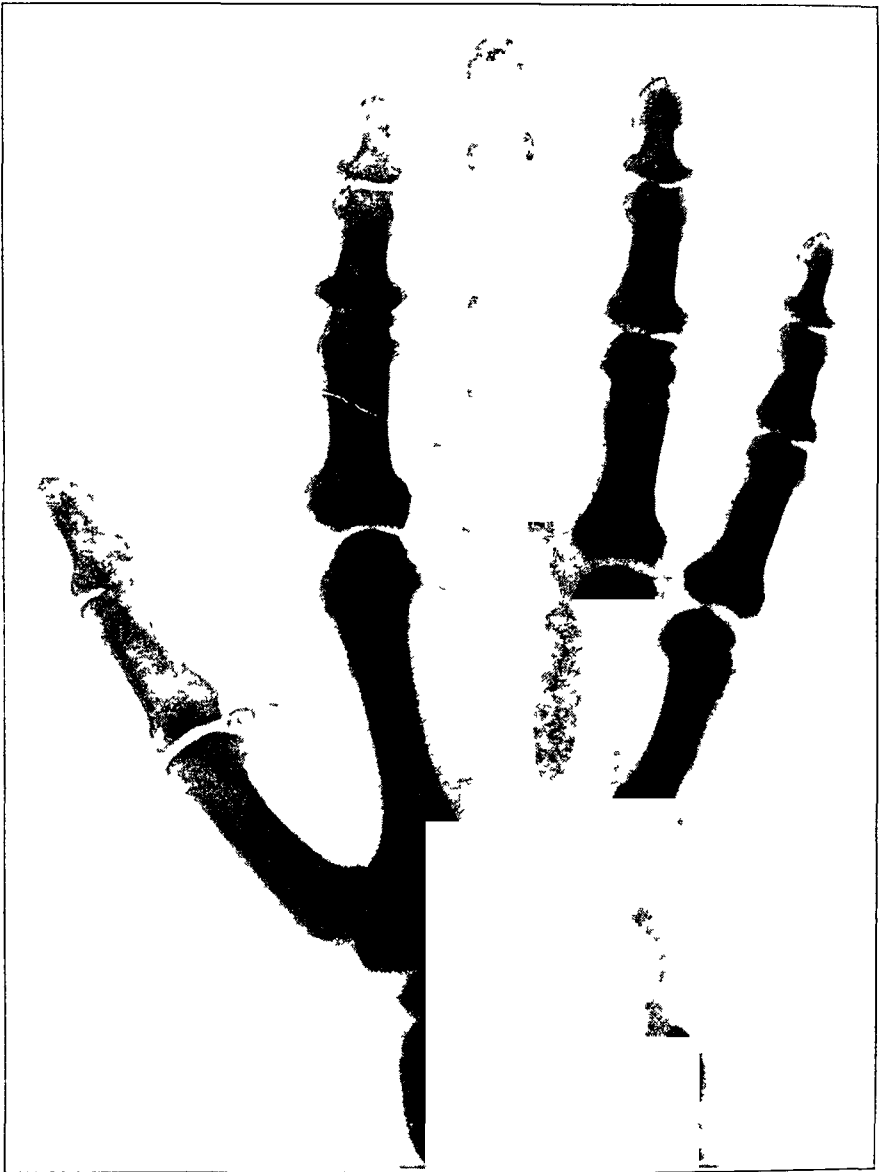


Fig 3—Acromegalic hand of patient shown in Figure 1, showing hypertrophic arthritis of hand and Heberden's nodes on fingers

or was there a prediabetic status which, due to his heavy overeating, precipitated the diabetes?

CASE 2—A woman, aged 41, having no familial history of diabetes, had acromegaly, which had developed twelve years before. Besides this she had had no previous illnesses except measles and influenza. Menopause occurred at the age of 37.

Glycosuria had been first discovered four years before I saw her, but other diabetic symptoms, itching of the genitalia, polyuria and thirst, had not developed until two years later. During these two years her weight had fallen from 198 to 135 pounds (89.8 to 61.2 Kg.)

Physical examination disclosed the following conditions which are of especial interest: Acromegalic facies, hypertrophied labia, small uterus, deep masculine voice, thick lips, wide shoulders, narrow hips, much enlarged hands and feet.

When she entered the diabetic hospital of the Cleveland Clinic her blood sugar was 400 mg per hundred cubic centimeters and she had a glycosuria of 8 per cent. The Wassermann reaction was negative. A phenolsulphone-phthalein kidney functional test showed an excretion of 40 per cent during the first hour, 20 per cent the second.

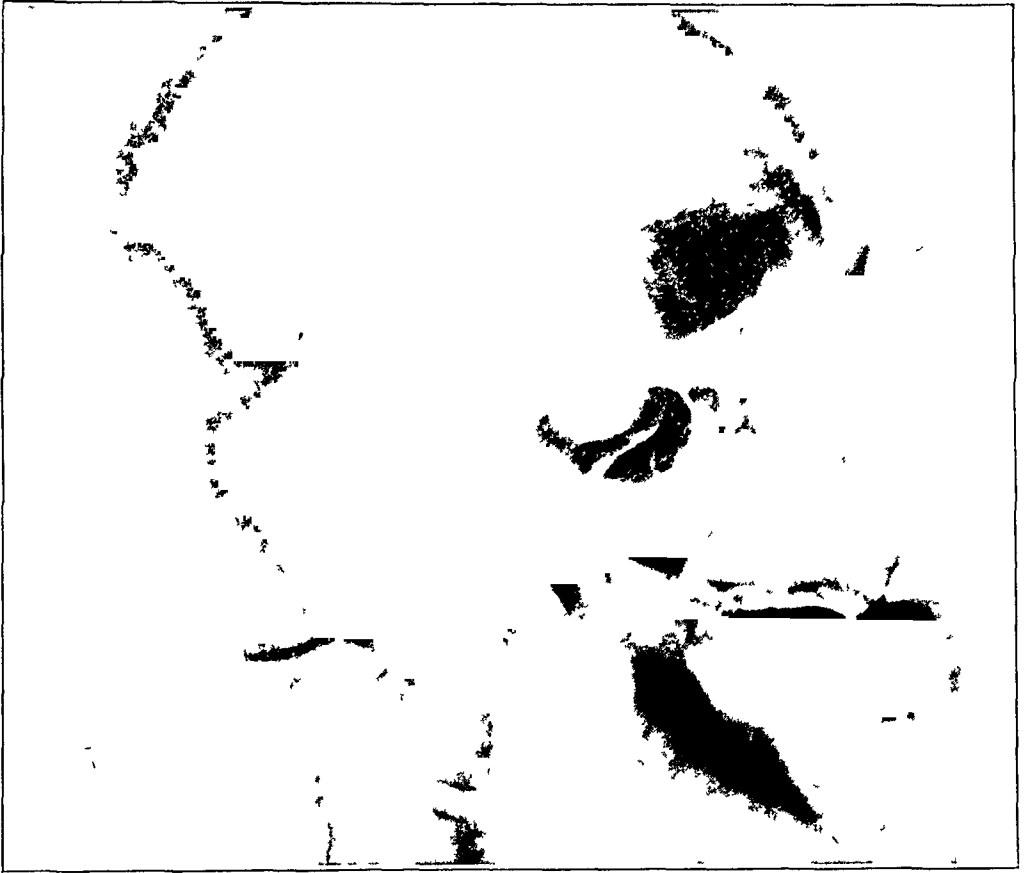


Fig 4—Skull of patient shown in Figure 1, showing large sella turcica

The graphic record (Fig 8) shows how a regulated diet plus insulin reduced the blood sugar to the normal level in two weeks, during which time the twenty-four hour urine sugar, which at first was as much as 56 Gm, disappeared entirely.

From time to time after her discharge from the hospital, friends of the patient reported to me that she would not adhere to the prescribed diet but was eating as she pleased and was not taking insulin regularly.

Fifteen months later I was called to see her at another hospital by a physician who had been summoned to take care of her some ten days previously because of a carbuncle which had developed on her buttock. At the time I saw her she was in deep coma, with blood sugar varying from 475 mg per hundred cubic centimeters in the morning to 810 mg the afternoon of the same day, heavy acetonemia was present and the plasma carbon dioxide amounted to a tension of 99 mm.

A 10 per cent glucose solution with insulin was administered intravenously, the patient rallied a little but died on the second day from acute dilatation of the heart, which developed when she began to struggle in an attempt to sit up

In this case, as in Case 1, acromegaly had preceded diabetes by a number of years and, as in the former case, we cannot say whether or

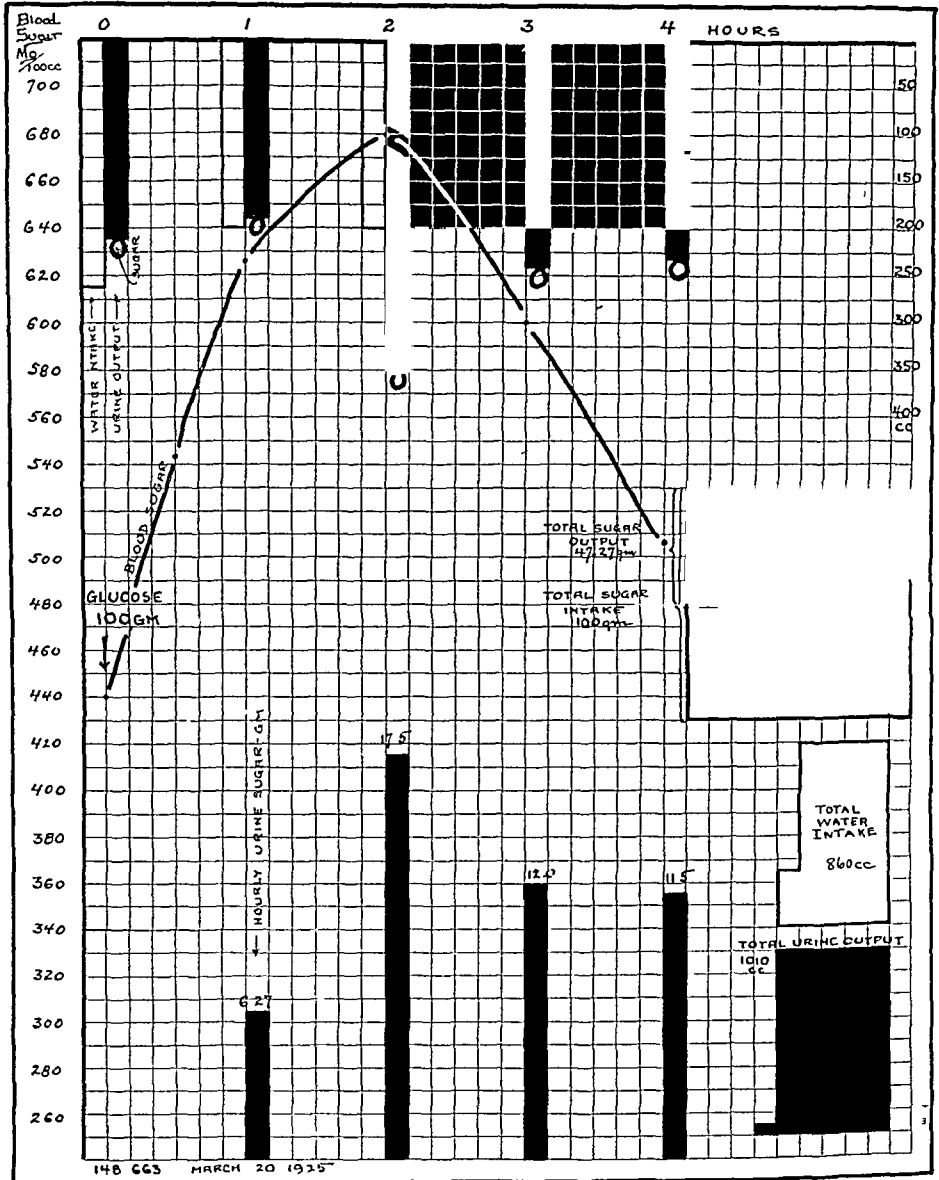


Fig 5—Glucose tolerance curve of patient with acromegaly associated with diabetes, showing high blood sugar content, examination revealed plasma chloride, 530 mg per hundred cubic centimeters, blood urea, 51 mg, blood uric acid, 27 mg, blood creatinine, 16 mg, blood nonprotein nitrogen, 55.1 mg, and plasma acetone, a trace

not the acromegaly itself had been a causative factor in the production of the diabetes. The history of this patient emphasizes the fact that the diabetes that develops in a case of acromegaly does not differ from

any other case of diabetes. The patient improves just as readily under proper treatment and retrogresses as promptly with lack of treatment. Insulin seems to be just as effective in these cases as it is in others.

Another case of acromegaly has recently come under my observation, and since the carbohydrate metabolism has been investigated, it is included here, although as shown by the glucose tolerance test, in this case diabetes is not associated with the acromegaly.

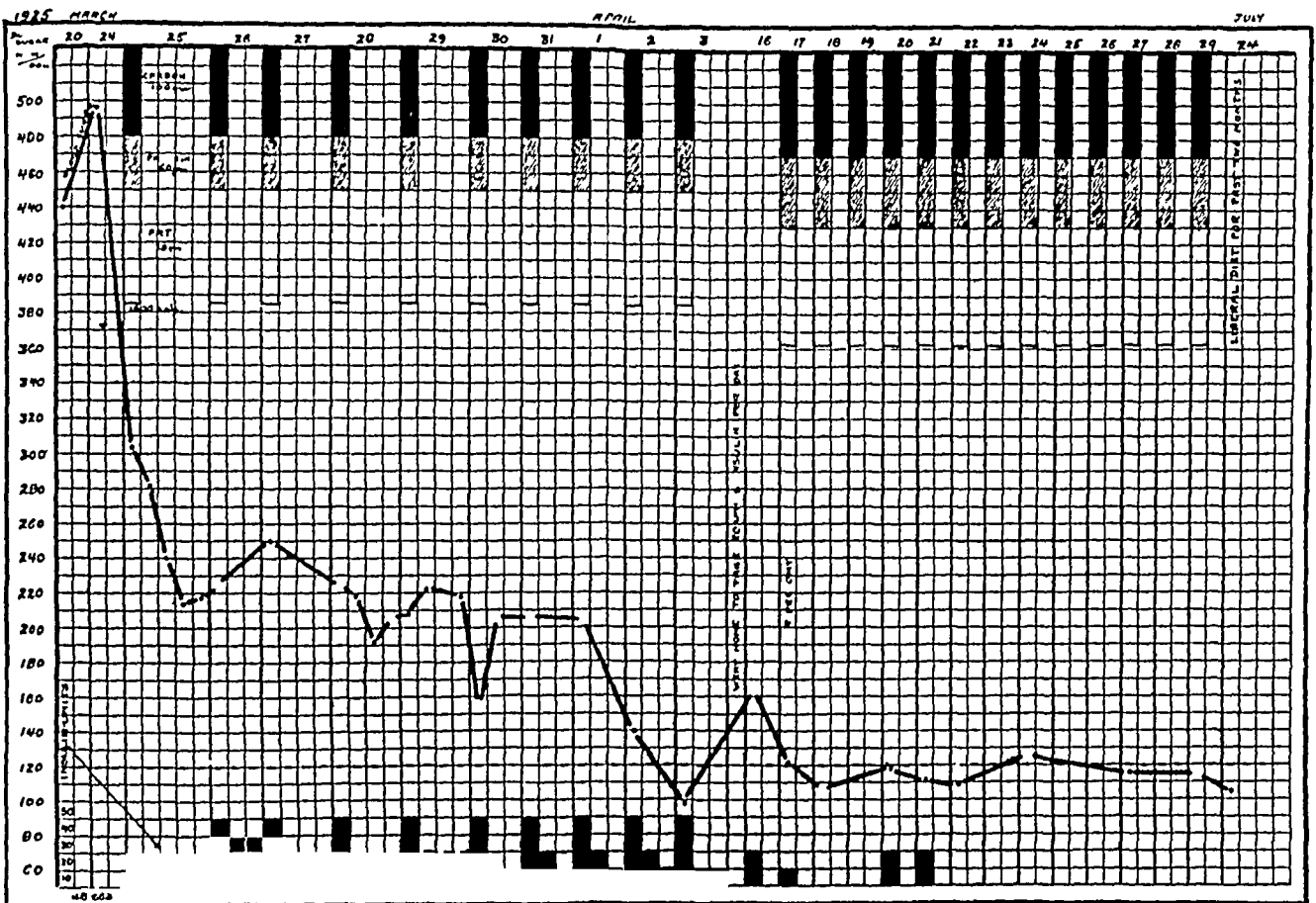


Fig 6 Daily blood sugar level of patient whose glucose tolerance curves are given in Figures 5 and 7, showing apparent disappearance of diabetes

CASE 3—A woman, aged 43, had been perfectly well in early life, had married at the age of 24, and since marriage had had only one menstrual period. For ten years she had had extremely bronzed skin. In 1916 she had had an attack of "painful joints," so severe that morphine had been required to control the pain. In 1918 she had had an attack of influenza after which she had been in a weakened condition for two years. This was followed by a marked change in her features, and enlargement of the hands. The size of her shoes increased from $5\frac{1}{2}$ to $8\frac{1}{2}$, she used to wear a No. 7 glove, but at this time could not get a glove that would fit her. Between 1910 and 1915 she had gained 45 pounds (20.4 Kg) in weight (Fig 9). In 1921 she had three attacks of renal colic and passed a stone. She complained of extreme thirst, to relieve which she drank large quantities of water.

Urinary examination showed no glycosuria. A roentgenogram showed an enlarged sella turcica. There was a change in the field of vision as indicated on the chart (Fig 10), with marked dimness of vision. She complained of marked headaches and of nocturia. The jaws were markedly prognathous, the teeth were spread, the nose and lips were abnormally large, and there was a marked growth of hair on the legs. The thyroid was not enlarged.

Although some of the symptoms in this case suggest diabetes, the presence of that condition was ruled out by the glucose tolerance test, although there was slight leaning toward impairment of carbohydrate tolerance (Fig 11).

In spite of the points emphasized by Cases 1 and 2, and of the lack of evidence of diabetes in Case 3, the striking frequency with which diabetes occurs in cases of acromegaly cannot be disregarded. Is it not possible that the factor that causes enlargement and hypersecretion

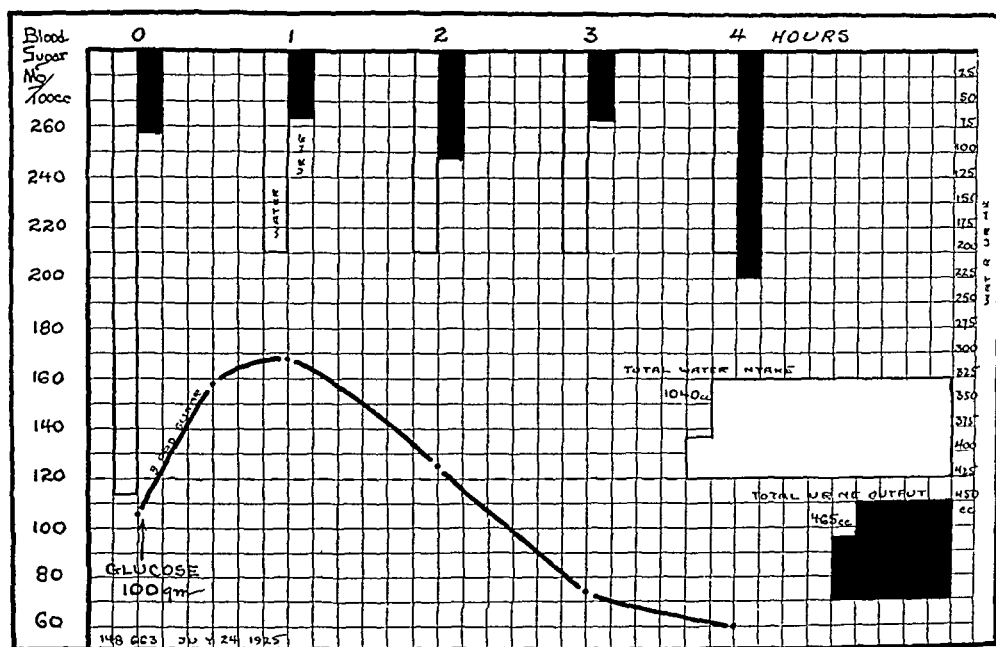
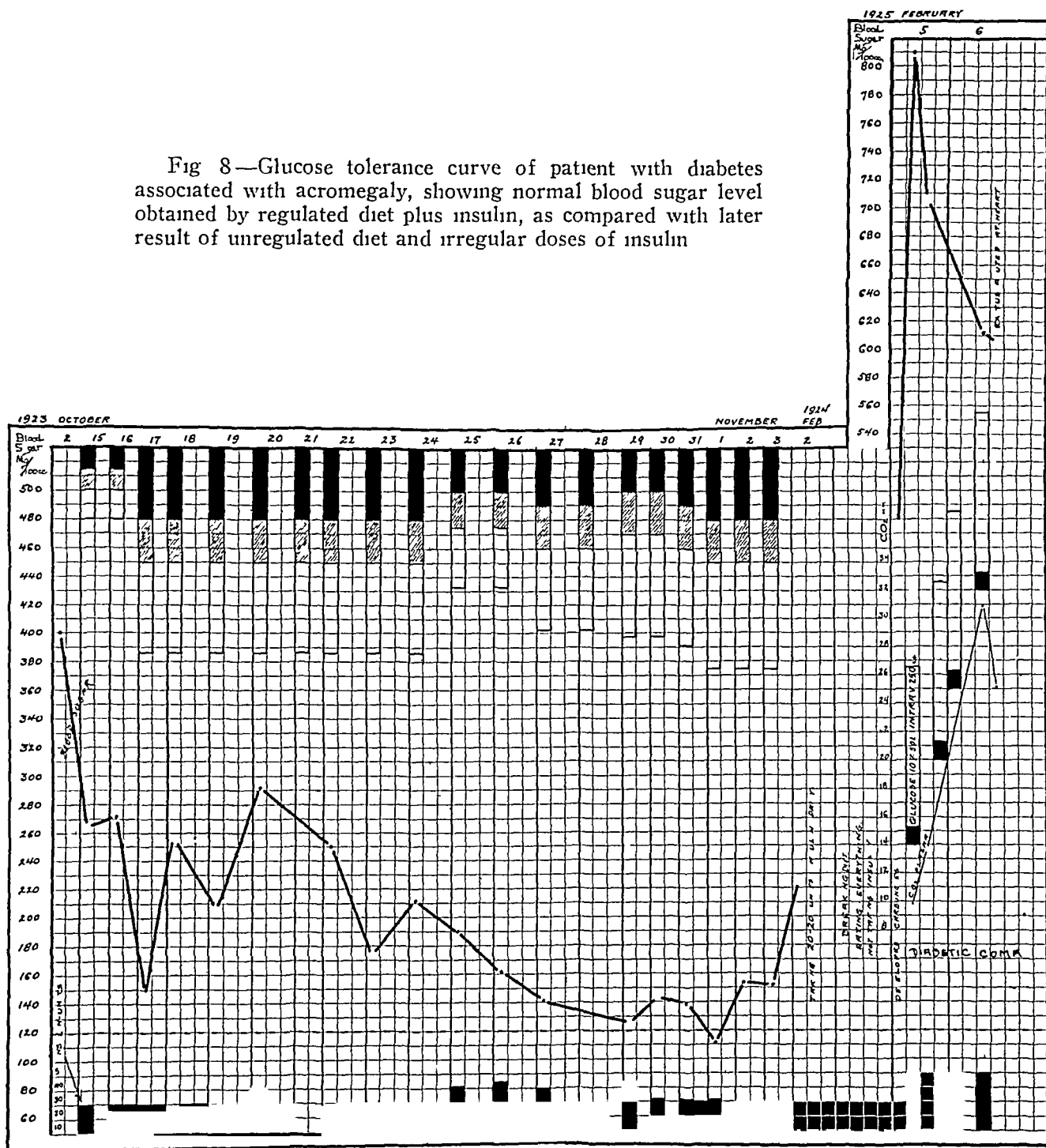


Fig 7—Normal glucose tolerance curve of patient whose curve is given in Figure 5, showing apparent disappearance of diabetes, examination revealed plasma chloride, 585 mg per hundred cubic centimeters, blood urea, 21 mg, blood uric acid, 19 mg, blood creatinine, 11 mg, nonprotein nitrogen, 257 mg, and plasma acetone, negative.

of the posterior part of the pituitary gland may also cause the disturbance of the insulogenic function of the pancreas? If the pituitary gland were primarily concerned in the production of diabetes, then such cases as those cited above should not respond to the ordinary treatment as readily as other cases, but such has not been our experience. Moreover, removal of the pituitary gland ought to cure diabetes in such cases, but unfortunately it does not. The occasional report of an improvement of the diabetic condition in these patients must be regarded with caution, for one encounters many atypical cases of diabetes as well as acromegalic diabetes such as von Noorden reports in his series. Such cases as

Fig 8—Glucose tolerance curve of patient with diabetes associated with acromegaly, showing normal blood sugar level obtained by regulated diet plus insulin, as compared with later result of unregulated diet and irregular doses of insulin



these reported here therefore only emphasize the complexity of this problem

REVIEW OF THE LITERATURE

In order to investigate the studies in this field, the literature has been searched and the following abstracts are offered as epitomizing all that I have been able to find regarding this subject

Chauffard,¹ in a clinical lecture on pituitary diabetes, reviews the general facts regarding this relationship. He states that the relationship between pituitary disturbance and diabetes insipidus is common, the first case recorded



Fig 9—Patient with acromegaly with suspected associated diabetes, showing acromegalic development of face and hands

having been reported by an Italian, Farini. As for the correlationship of acromegaly and diabetes mellitus, he asserts that the first case of this kind was observed in his clinic in 1899-1900, and reported by Ravaut. The patient was a woman, aged 29, who at 21 had developed acromegaly with cessation of menstruation. Pituitary extract was administered without any result. The disease progressed during the next five years, and she became obese, her weight increasing to 83 Kg (182.6 pounds). At this time severe headaches developed, left visual disturbance, great thirst, polyuria, pruritus vulvae and a loss of 19 Kg (41.8 pounds) in weight. She was several times on the verge of coma, the condition yielding to massive alkalization, but she soon succumbed to pneumonia.

1 Chauffard. Pituitary Diabetes, M. Press, London, 110 142, 1920

Postmortem examination revealed a fungating tumor the size of a walnut situated in the pituitary gland and adherent to the sella turcica. A histologic examination of the gland showed it to be an adenoma with sarcomatous elements, a type of tumor that is supposed to increase the function of the gland, causing hyperpituitarism. The medulla and fourth ventricle were healthy. All the other organs were hypertrophied, including the pancreas, which weighed 90 Gm. The heart was hypertrophied, the liver weighed 2.8 Kg, the spleen 200 Gm, the kidney 320 Gm. The small intestine measured 101 meters, the appendix 13 cm. "As the patient's growth had come to an end, and she could not develop into a giant, the developmental energy had been concentrated on the viscera," says the author.

Of especial importance is the recent exhaustive article by Sachs and MacDonald,² who state that in accordance with their views in regard to glycosuria, the various investigators in this field may be divided into three groups. "First, those who assume a center in the neighborhood of the hypophysis, as claimed by

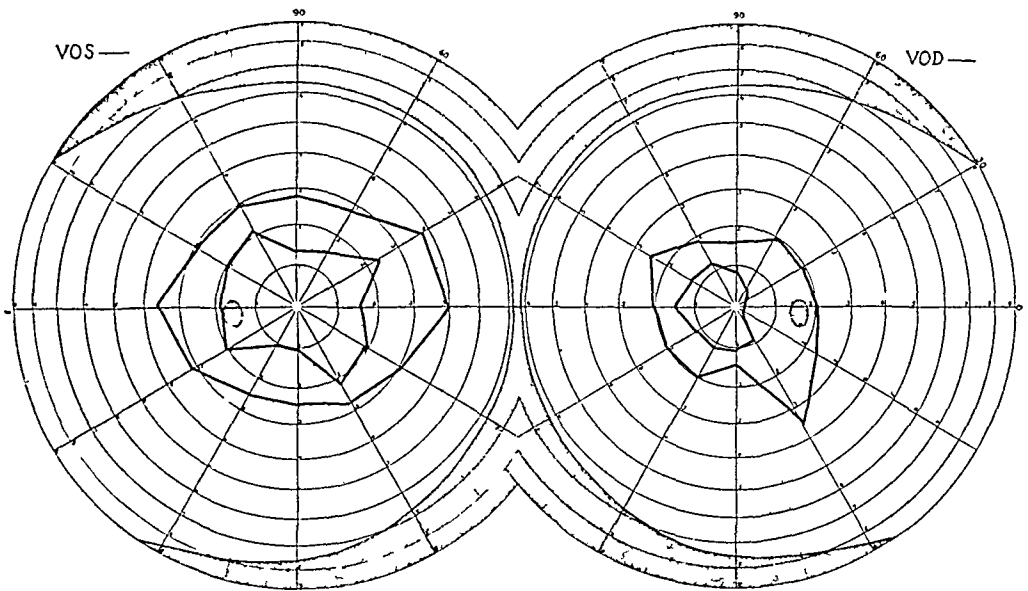


Fig 10—Change in field of vision in patient shown in Figure 8

Rath, Loeb and more recently by Aschner. Second, those who think that the glycosuria is due to secondary changes in the other ductless glands, notably the pancreas—Pineles, Hausemann and Dallemange—who found atrophic changes in the pancreas, and Lorand who assumes that the sugar is the result of changes in the thyroid due to an interrelation with the hypophysis. Third, those who hold that the glycosuria is directly due to the increased production of some substance in the pituitary gland which is the active agent in producing the condition," notably Naunyn, Borchardt, Bernstein and Falta.

They cite the findings reported by Houssay, Hug and Malamud that there is no marked difference in carbohydrate metabolism in dogs after the pituitary gland has been removed. Sachs and MacDonald state that their studies of glucose tolerance and of the response to insulin show that diabetes in cases of pituitary dysfunction is similar to diabetes in those cases in which the primary cause is a lesion in the pancreas. They cite a case reported by Blum and Schwab³ in which

2 Sachs, E, and MacDonald, M. E. Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions (with bibliography), *Arch Neurol & Psychiat* **13** 335-368 (March) 1925

3 Blum, L, and Schwab, H. Diabète acromégalique et insuline, *Compt rend Soc de biol* **89** 195, 1923

Various authors report that polyuria may be checked by lumbar puncture. Sachs and Macdonald also refer to the work of Camus, Gournay and LeGrand, who state that a lesion of the tuber cinereum in rabbits produces glycosuria which lasts for several months. These authors cite the work of Keeton and Becht, who found hyperglycemia following hypophysectomy.

The authors offer the following conclusions:

1 Complete removal of the pituitary gland does not lead to the death of the animal if the hypothalamus is not injured.

2 Their experiments confirm the conclusions of others that polyuria is apparently due to hypothalamic injury.

3 The average blood sugar level in fasting animals is slightly lower after pituitary or hypothalamic operation, but this level may be within the normal limits of variation.

4 Although transient glycosuria and hyperglycemia for from one to two days occurred after hypothalamic puncture in a few cases, they do not consider this of great importance.

5 They were unable to produce a permanent glycosuria experimentally, although it has been observed in cases of pituitary disease, some of which, though not all, were due to hyperfunction of the anterior lobe, which cannot be produced experimentally.

6 In all cases except those in which the anterior lobe had been removed, the maximum height of the blood sugar curve was reached at the end of one hour in contrast to the curve in normal animals in which the maximum height occurs at the end of one-half hour.

7 The blood sugar curve in the cases in which the anterior lobe had been removed was of the normal type.

Goetsch, Cushing and Jacobson (reported by Ellis⁵) have demonstrated the "occurrence of glycosuria after handling and electrical stimulation of the pituitary body, and of an increased carbohydrate tolerance in animals after hypophysectomy," thus supporting "the theory developed from clinical observations that both acromegaly and glycosuria result from overactivity of the hypophysis."

Froment (reported by Ellis) was unable to find any case in which glycosuria was associated with hypophyseal tumors in the absence of acromegaly, while, on the other hand, Anders and Jameson⁶ compiled a number of cases of lesions of the pituitary body in which glycosuria was present although there was no acromegaly. Ellis states, however, that a careful analysis of their data shows that in the majority of cases the "glycosuria was transient or terminal and associated with either marked intracranial pressure or injury to the base of the brain."

In an experimental study of the effects of the hypodermic injection of hypophyseal extract, Claude and Baudouin⁷ found that a varying degree of glycosuria was produced, the most marked glycosuria being obtained in cases of arthritis and in a prediabetic condition. The maximum degree of glycosuria was obtained when the extract was injected before a meal, while the response was feeble when the meal was taken from one-half to one hour or more before the injection. When the meal was taken from two and one-half to three hours before the injection, the degree of glycosuria was very slight. The authors

5 Ellis, A. W. M., and Trumbull, H. M. Hyperglycemia and Glycosuria in Acromegaly, *Lancet* **1** 1200-1203 (June 14) 1924.

6 Anders, J. M., and Jameson, H. L. The Relation of Glycosuria to Pituitary Disease and the Report of a Case with Statistics (with bibliography), *Am J M Sc* **148** 323-329, 1914.

7 Claude, H., and Baudouin, A. Le mecanisme de la glycosurie hypophysaire, *Compt rend Soc de biol* **73** 568-570, 1912.

explain this phenomenon by the statement that the glycosuria is due to some type of liver insufficiency as the result of which the glucose is not transformed into glycogen, for, as they state, were the injection of the extract to bring about the mobilization of sugar in the blood it should be equally effective regardless of meals

From experiments on rabbits, Borchardt⁸ found that the injection of hypophyseal extract produced glycosuria and in his last two cases hyperglycemia also was produced. He searched the literature to find how many cases in which diabetes was associated with acromegaly had been reported in the hope of ascertaining whether the glycosuria found in acromegaly is due to a hyperfunction or hypofunction of the hypophysis. He compiled from the literature 176 cases of acromegaly among which diabetes was present in 35.5 per cent. In eight other cases a limited degree of glycosuria had been reported. Altogether there were seventy-one cases, or 40.32 per cent, which showed a pathologic weakness of the carbohydrate metabolism. The degree of impairment varied from slight alimentary glycosuria to coma. In 1897 Strumpell⁹ described a case in which the glycosuria disappeared entirely in spite of the large carbohydrate intake, and later reappeared without any apparent reason, again disappearing shortly before death, and von Noorden¹⁰ says that of his four cases of acromegaly-diabetes, only two followed a normal course, the two other cases showing fluctuations of the glycosuria which were entirely independent of the food intake and indicated the influence of some other undiscovered factors.

Borchardt,¹¹ in another article, cites the work of Hausemann and Dallemagne, who found in the majority of their cases that the pancreas was histologically normal, and of Benda,¹² who described a case of acromegaly with involvement of the pancreas but without diabetes.

Borchardt makes an observation that has been verified by numerous authors, that in all acromegaly-diabetes cases there was a hypoplastic tumor of the hypophysis, while in acromegaly without diabetes the hypophysis had often degenerated, which certainly strongly suggests a relationship between hyperfunction of the hypophysis and diabetes. The author endeavored to prove this by the injection of hypophyseal extract in rabbits, thus producing both glycosuria and hyperglycemia. He thinks that one should be cautious in deciding whether or not diabetes is always latent in acromegaly and also whether or not it is ever completely cured, as in many of the cases cited, there was but a single urinary examination. Glycosuria is more frequently found in acromegaly than in any other disease. In most of the reported cases, however, the pathologic examination did not reveal any involvement of the pancreas.

Borchardt concludes that the simplest explanation for diabetes in association with acromegaly is that it is due to an increased secretion of the hypophysis, as the hypophyseal tumor degenerates this secretion ceases, and may bring about cessation of the diabetes.¹³

It appears that the majority of authors accept the theory advocated by Loeb in 1898, that diabetes in acromegaly is due to pressure of the hypophyseal tumor on a hypothetical sugar centrum in the brain, the seat of which he

8 Borchardt, L. Experimentelles über den Diabetes bei der Akromegalie, *Deutsch med Wchnschr* **34** 946, 1908

9 Strumpell, A. Ein Beitrag zur Pathologie und pathologischen Anatomie der Akromegalie, *Deutsch Ztschr f Nerven* **11** 51-87, 1897

10 Von Noorden, C. Die Zuckerkrankheit und ihre Behandlung, Berlin, 1910,

11 Borchardt, L. Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, *Ztschr f klin Med* **66** 332-348, 1908

12 Benda, C. Beiträge zur normalen und pathologischen Histologie der menschlichen Hypophysis cerebri, *Berl klin Wchnschr* **37** 1205, 1900

13 The table accompanying Borchardt's article includes a complete summary of the cases of diabetes associated with acromegaly

placed in the region of the tuber cinereum. This theory, however, does not explain why, in certain cases of hypophyseal tumor without acromegaly, no diabetes occurs. Many authors cite the experience that in all cases of acromegaly complicated with diabetes there is a hyperplastic tumor of the hypophysis, whereas in cases of acromegaly without diabetes one often finds degeneration of the hypophysis, which points to the interdependence of hyperfunction of hypophysis and diabetes, this is in full harmony with the pathologic-anatomic findings. Cases of acromegaly investigated by Benda show a transition of hyperplasia of the hypophysis to adenoma and finally to sarcoma. This would explain why diabetes in acromegaly so often disappears later, as soon as the increased production of the hypophyseal secretion has ceased.

Kollarits¹⁴ reported fifty-one cases of hypophyseal tumors without acromegaly, not one of which developed diabetes. Such a varying relationship of hypophyseal tumors to acromegaly does not seem to be in harmony with Loeb's theory.

Lorand¹⁵ advanced another theory in which he suggests that diabetes in cases of acromegaly is due to an increased function of the thyroid and its influence on the pancreas. From the fact that thyroid changes are often present in acromegaly, Lorand concludes that they precede and perhaps cause the changes in the hypophysis.

Camus and Roussy,⁴ in their experimental researches on the pituitary body in dogs, found that the occurrence of polyuria after hypophysectomy depended on whether or not the base of the brain had been injured. To verify this finding they injured the base of the brain without injuring the hypophysis and a marked polyuria resulted. They found that the protraction of polyuria from this cause varied, lasting from a short time to many months. Glycosuria followed in one dog in which the polyuria had persisted for seven months. The administrations of pituitary extracts were ineffectual. The optopeduncular region which lies at the level of the tuber cinereum in the vicinity of the infundibulum was the only zone within which a lesion was followed by polyuria.

These authors conclude (1) that neither the partial removal of one or of both lobes nor total removal of the pituitary body either modifies appreciably the tolerance to carbohydrates or causes the appearance of alimentary glycosuria, and (2) "that the injections of concentrated extracts of the posterior lobe, of the anterior lobe or of the whole hypophysis, do not sensibly modify—in the animals operated on—the limit of tolerance to carbohydrates," after the operative procedures described in the foregoing.

An interesting instance of the occurrence of hyperglycemia and glycosuria in a case of acromegaly has recently been reported by Ellis.⁵ The facts of the case are briefly these. A woman, aged 42, had a blood sugar of 430 mg per hundred cubic centimeters, and heavy acetonemia. On three days fasting she became sugar free. Her diet was gradually raised to 83 Gm of carbohydrate, 44 Gm of protein, 76 Gm of fats, a total of 1,200 calories—a very low diet—and a hypophysectomy was performed, two, five and fifteen months after which the blood sugar was, respectively, 150, 120 and 130 mg per hundred cubic centimeters. Two and three years later glucose tolerance tests gave the following results: (a) blood sugar before ingestion of 50 Gm of glucose, 147 mg per hundred cubic centimeters, three-quarters of an hour after, 270 mg per hundred cubic centimeters, two hours after, 220 mg per hundred cubic centimeters, (b) blood sugar before ingestion of 50 Gm of glucose, 180 mg per hundred cubic centimeters, three-quarters of an hour after, 220 mg per hundred cubic centimeters, and two hours after, 230 mg per hundred cubic centimeters.

14 Kollarits, J. Hypophysistumoren ohne Akromegalie, *Deutsch Ztschr f Nervenhe* 28 88-105, 1905.

15 Lorand, A. Pathogénie du diabète dans l'acromegalie, *Compt rend Soc de biol* 56 554, 1904.

The author does not consider this as a case of diabetes, but rather as a disturbance of carbohydrate metabolism due to some obscure cause. To quote his words: "As will be seen by the case here reported, it (glycosuria) may, however, attain the proportions of a true diabetes, and in the literature can be found reports of cases showing all the symptoms and complications of that disease." "Though ketonuria is stated to be rare in acromegaly, Froment (*J Neurol* 29 664, 1922) has been able to collect a dozen instances in the literature, in which death from typical diabetic coma has ensued." "It is generally stated, perhaps on somewhat meager evidence, that the glycosuria of acromegaly is singularly insusceptible to changes in diet, in our patient no support for this statement was found, the urine became sugar-free on fasting as rapidly as would be expected in a true diabetes of equal severity." "The relatively satisfactory carbohydrate metabolism following removal of the hypophysis, in the case described above, suggests that in this patient the glycosuria was not due to pancreatic deficiency," and he tries to explain the condition as being due to the fact that pituitary extract counteracts the action of insulin as shown by Burn in his work on rabbits.

If we analyze the data on this case reported by Ellis, I think that we can assume with a fair degree of accuracy that it was a case of diabetes, for we know that there is in certain cases an association of these two conditions, acromegaly and diabetes. Were one given the laboratory and clinical data by themselves, I think no one would hesitate for a moment to make a diagnosis of diabetes. The curves of the two glucose tolerance tests, done a year apart, closely simulate diabetic curves, although unfortunately the author stopped his observations at the end of the second hour, which is not a long enough period to furnish final information. Fasting produced a sugar free condition, it always does in a diabetic patient. A low diet for a time kept the sugar in check, as one would expect in a case of diabetes. Hypophysectomy was performed and the author attributes all the progress to this operation. I have serious doubts about this point since the patient was under a diabetic regimen. Moreover, later a progressive hyperglycemia developed, the fasting blood sugar in 1921 was 150-120 mg per hundred cubic centimeters, in 1922, 130 mg, in 1923, 150-140 mg, and in 1924, 180 mg, a progressively diminishing carbohydrate tolerance which, if it keeps on, is bound again to bring the patient into a severe diabetic condition, even though the pituitary gland has been removed. Diabetes is diabetes, whatever be the primary cause. That the pituitary gland may play some part in its causation, no one can deny, but we have still to prove that hypophysectomy will cure diabetes in the case of acromegaly.

Brooks¹⁶ reports an interesting case of acromegaly in a man aged 30. The patient was an Englishman whose head was injured in 1891, he was in good health subsequently until 1896, when acromegaly became manifest. During the later year he was treated for syphilis which was supposed to be of recent

16 Brooks, H. A Case of Acromegaly, with Autopsy, New York M J 65 418-421, 1897

origin Two months before he was seen by the author he was treated unsuccessfully for syphilitic iritis At this time he developed marked thirst, shortly afterward becoming drowsy and irritable "He had attacks of dyspnea, some of long duration" Finally, one day after a short walk he went into a state of collapse, and the next morning was still in a stupor, although he could be aroused His tongue was coated and dry, the skin was cyanotic, the pulse was feeble and rapid, the abdomen was distended and tympanitic, there was an acetone odor on the breath, the right pupil was dilated and did not react to light, the left pupil was normal, the temperature was normal The urine contained 75 per cent sugar The stupor gradually deepened, and he died the next morning

The postmortem examination revealed a tumor of the hypophysis, an ovoid red mass, measuring 15 cm from before backward and 07 cm from above downward It was attached below, apparently, to the pituitary body The mass was of a soft jelly-like consistency, and was quite vascular It was found to press directly on the left optic tract just posterior to the chiasm The tumor was attached to the hypophysis, which was enlarged to about five times its volume The pituitary fossa was greatly enlarged, and the bones making up its wall were abnormally thin No adhesions existed between the pituitary body or the tumor and the surrounding tissues

Hausemann, reported by Chadbourne,¹⁷ thinks it is not unlikely that an intimate relation exists between acromegaly and diabetes, and although diabetes was stated to have been present in only twelve of the ninety-seven undoubted cases of acromegaly that he was able to find in the literature, these cases were those which had been most accurately observed

Chadbourne reports the case of a man, aged 40, who at the age of 19 "began to have sick headaches every few weeks" These attacks became less frequent after he was 24 years old and had been absent during the last four years When he was 25 years old his hands and jaw began to get larger At the age of 36, his appetite increased markedly and he began to have great thirst and to pass large amounts of urine, these symptoms, together with itching of the skin, had persisted During the last four years he had lost 79 pounds (35.8 Kg) in weight When seen by the author he complained of failing eyesight The urine contained a large amount of sugar At this time his weight was 211 pounds (95.7 Kg), his height, 6 feet, 3 inches (190.5 cm), and he had the typical acromegalic facies The author says nothing about diabetic treatment but the description is significant

Machwitz¹⁸ reported a case of acromegaly-diabetes in a man aged 46 The acromegaly started when he was 22 years old, but the onset of diabetes dated back only two years The patient had a heavy glycosuria not related to carbohydrate intake, but he had no acidosis Roentgen-ray examination showed enlargement of the sella turcica, no bitemporal hemianopsia and only slight disturbance of vision It is interesting to note that an 18 year old son of the patient also had acromegaly

Lereboullet¹⁹ has described a case, the circumstances of which appear to confirm the assumption that the alimentary glycosuria or diabetes sometimes associated with acromegaly is due to nerve irritation at the floor of the third ventricle, produced by enlargement of the sella turcica The author believes that in contrast to diabetes insipidus, which is due to the pituitary gland itself, the glycosuria type of diabetes seems to be the result of irritation in the vicinity of the pituitary gland but not within the gland itself

17 Chadbourne, T L A Case of Acromegaly with Diabetes, New York M J **67** 449, 1898

18 Machwitz Akromegalie, kombiniert mit Diabetes, Munchen med Wchnschr **67** 198, 1920

19 Lereboullet, M Diabete et acromegalie, Progres med **35** 106-108 (March 6) 1920, abstr, J A M A **74** 1356 (May 8) 1920

Labbe and Langlois²⁰ report the case of a man, aged 48, who had hypertrophy of the pituitary gland with acromegaly and also presented symptoms of diabetes, but there was no diminution in weight and pituitary treatment did not affect the polyuria. "The glycosuria, however, was markedly influenced by pituitary treatment, plus reduction of the intake of carbohydrates, the sugar in the urine dropping from 129 mg per hundred cubic centimeters to zero in four months." This case also seems to confirm the conclusion of the authors "that not the pituitary gland itself, but an irritation of some center in the base of the brain is responsible for the production of diabetes and polyuria."

Van Nuys²¹ has reported a case of diabetes of four years' duration with a loss of 100 pounds (45.4 Kg) in weight in a patient in whom the presence of hyperpituitarism was suggested because of her facies and the heavy glycosuria. She had "heavy cheek bones, a broad nose and undershot jaw." The breath had an acetone odor. "Repeated roentgenograms of the skull seemed to show a much enlarged sella turcica, the shadows, however, were obscure as if a growth partly obliterated the outlines of the region." He says that pituitary extract was given without appreciable effect. The Allen treatment for diabetes and potassium iodide were of benefit, and from a state of coma, because of which the author was first consulted, the patient improved until she was able to sit up and walk a little when she left the hospital.

Anders and Jameson²² report the case of a woman, aged 46, weighing 170 pounds (77.1 Kg), who had a large gangrenous ulcer in the palmar surface of the hand which extended slowly until death occurred. Throughout her illness she had polydipsia, polyuria and glycosuria, from 5 to 7 per cent. The glycosuria appeared two years after the onset of a typical acromegaly. She also had hyperthyroidism. She died in coma a month after she was first seen by the authors. They cite the statement by Dock that diabetes arising in the course of acromegaly is cerebral and due to the pituitary disease as is shown by the fact that "diabetes is most marked with the largest tumors."²²

Grenet and Tanon²³ report a case of acromegaly with diabetes in a woman, aged 50. She had the typical acromegalic features, which had been developing over a period of seventeen years. The vision of the right eye was completely lost, and the left eye did not distinguish objects situated at the extreme left of the visual field. The eye examination revealed double optic atrophy, complete on the right, incomplete on the left, temporal hemianopsia of the left eye, external strabismus of the right eye, no paralysis of the ocular muscles. The urine showed a heavy glycosuria, and she had some diabetic symptoms. For several years she had had polydipsia, drinking from 2 to 3 liters of water daily. Her appetite was good but not exaggerated. The urine output was 3 liters a day. The glycosuria had apparently existed for the preceding seven months, as examination of the urine before that time had revealed no sugar. Under treatment the glycosuria decreased from 66 to 32.72 Gm a liter.

This case is of interest because of the late appearance of the glycosuria though the acromegaly had been present for seventeen years.

Koopman²⁴ cites from the literature a number of cases of acromegaly in which the patients died in diabetic coma (Stricker, Bury, Stadelmann, Strumpell, Hinsdale, Ravaut, Dallemange, Umber).

20 Labbé, M., and Langlois, S. Acromégalie et diabète, *Bull et mem Soc med d hôp de Paris* **43** 229-233 (March 7) 1919, abstr, *J A M A* **72** 1796 (June 14) 1919.

21 Van Nuys, F. Case Report of Hyperpituitarism and Hyperglycemia, *Boston M & S J* **181** 465-466 (Oct 9) 1919.

22 This article is accompanied by an excellent table of reported cases of acromegaly with glycosuria compiled from the literature.

23 Grenet, H., and Tanon, L. Acromégalie et diabète, *Rev Neurol* **15** 84-86, 1907.

24 Koopman, J. Hypophysaire diabetes, *Nederlandsch Tijdschr v Geneesk* **2** 1071-1076 (Oct 11) 1919.

He speaks of a remarkable case of diabetes with acromegaly described by Stricker in the Dutch literature. In this case marked lipemia was present and the urine contained a large amount of acetone and diacetic acid. Coma was expected, but the patient died of paralysis of the heart. "Generally," says Koopman, "the diabetes as it is seen in cases of acromegaly, is not absolutely identical with the diabetes we generally see. Lery thinks it better not to speak of diabetes in these cases, but to call it glycosuria. The complications frequently seen in diabetes mellitus, as furunculosis, pseudotabes and arthritis, occur also in these cases but not so often."

Koopman cites a case of syphilis of the pituitary gland described by Cushing which presented a typical clinical picture of diabetes mellitus. Koopman also reports two cases of his own, in one of which the glycosuria was relieved by treatment with hypophyseal extract, in the other the patient improved at first but later refused to diet and to take the hypophyseal extract and died in coma.

A striking feature in these cases was the low protein tolerance. The author thinks that, while it cannot be proved that the diabetes was of pituitary origin, yet that the hypophysis certainly played a prominent rôle in the production was proved by the fact that the patients responded so well to treatment with pituitary extract.

Blum and Schwab³ have presented two cases which offer an interesting comparative study of diabetes with and without acromegaly. Both patients received

TABLE 2—*Response of Two Patients of Blum and Schwab to Thirty Units of Insulin*

Time	Diabetes With Acromegaly			Diabetes Without Acromegaly		
	Blood Sugar, Mg per 100 Cc	Urine		Blood Sugar, Mg per 100 Cc	Urine	
		Volume, Cc	Glucose per Liter		Volume, Cc	Glucose per Liter
8 35 a m	301			325		
9 00 (30 units of insulin administered)						
11 00	180	720	3	244	780	21
1 30 p m	173	430		160	290	13
3 30	251	320		155	400	
		670			190	

the same treatment except that the patient with acromegaly, who had an immense appetite, received potatoes during the noon meal. The response of each of these patients to the injection of 30 units of insulin is shown in Table 2.

The authors conclude that the presence of acromegaly does not affect the reaction to insulin.

Allen²⁵ reports the presence of acromegaly with marked glycosuria in a woman, aged 50. Thirst and weakness were of recent onset, within the preceding six months, while the acromegalic features began to develop ten years before. She was passing from 3,720 to 8,940 cc of urine daily and excreting from 200 to 480 Gm of sugar, the specific gravity being from 1.035 to 1.043.

Carnot, Rathery and Dumont²⁶ describe a case of diabetes in a woman with the typical acromegalic facies, in whom roentgen-ray examination showed destruction of bone about the sella turcica, with considerable enlargement of the gland. The patient, who was 58, had developed diabetes three years before, the onset being marked by a large appetite, thirst, loss of strength and large quantities of sugar in the urine. Later she developed severe headaches but there was no vomiting. Two months before diplopia had appeared. The

25 Allen, W. Acromegaly with Marked Glycosuria, Glasgow M J 66 166-169, 1906

26 Carnot, Rathery, and Dumont, J. Acromégalie, diabète, tumeur hypophysaire, Bull et mém Soc méd d hôp de Paris 35 921-935, 1913

menopause occurred at the age of 42. The patient suddenly developed a fever and died. At necropsy the sella turcica measured 0.032 by 0.025 cm., and the hypophysis was enormous, weighing 14 Gm. Microscopic examination did not reveal any normal hypophyseal structure. The pancreas weighed 100 Gm., and autodigestion had taken place, but the islands of Langerhans were visible and quite numerous.

Verger, Massias and Auriat²⁷ report a case of acromegaly in which the carbohydrate tolerance was exaggerated and there was no reaction to the extract of the posterior lobe of the hypophysis.

The patient was a woman, aged 36, who for thirteen years had had epileptic attacks and a modified acromegaly limited to impairment of sight and hirsutism, the feet and hands remaining normal. Roentgen-ray examination of the skull showed enlargement of the sella turcica. There was no adiposity, no change in stature, no polyuria and no glycosuria. She was able to tolerate from 100 to 300 Gm. of glucose a day without glycosuria. After injection of 0.2 Gm. of posterior lobe extract and absorption of the carbohydrate meal, no glycosuria followed, and there was no increase in the excretion of urine.

This was a complex case of bilobar dysfunction of the hypophysis, the dysfunction of the anterior lobe producing the acromegalic symptoms while the dysfunction of the posterior lobe produced exaggerated carbohydrate tolerance and was the cause of the absence of reaction to the injections of extract of that lobe.

Variations in the incidence of glycosuria in cases of acromegaly are described in the literature. Thus, in a case described by P. Marie (cited by Borchardt⁸), glycosuria was present only once while the patient was on a full diet, but it appeared when the diet was sugar free. This occurrence of glycosuria independently of the diet is noteworthy. As noted above, in 1897 Strumpell described a like case, in which glycosuria disappeared in spite of a diet rich in carbohydrates, and reappeared later without any apparent reason, disappearing again shortly before death. Such cases are far from rare. Two of the four diabetic-acromegalic cases cited by von Noorden followed a normal course. In two others glycosuria appeared and disappeared again, regardless of the diet.

CONCLUSIONS

The following conclusions are drawn from personal experience with the two cases here reported, in which diabetes was associated with acromegaly, and from a study of the literature.

1 In general, hypopituitarism is accompanied by an increased carbohydrate tolerance and hyperpituitarism by decreased tolerance, but this is not an absolute rule.

2 In the majority of cases of so-called diabetes associated with acromegaly that have been reported in the literature, especially in older cases, the diagnosis of diabetes was made on the basis of urine exami-

²⁷ Verger, H., Massias, C., and Auriat, G. Exageration de la tolérance aux hydrates de carbone et absence de réaction à l'extrait de lobe postérieur de l'hypophyse chez une acromégalie, *Compt. rend. Soc. de biol.* **87**: 197, 1922.

nation only Since glycosuria does not always indicate diabetes, this should be borne in mind in evaluating these reports

3 In most reported cases and in the two here reported, the onset of acromegaly preceded the onset of diabetes by many years

4 The treatment of diabetes associated with acromegaly does not differ from the treatment of the ordinary case, and the response of the former type of case does not differ from that of the ordinary case

5 Patients in whom diabetes is associated with acromegaly if not controlled are as subject to acidosis and coma as the ordinary case

6 Hypersecretion of the posterior part of the pituitary gland seems to produce hyperglycemia and glycosuria Whether this is the predisposing factor is not certainly established, the incidence of diabetes in acromegaly is rather high but, whatever the primary factor, the metabolic disturbance is due to a decreased insulogenic secretion It may be that the factor that produces hyperpituitarism may also have some influence in producing the decreased insulogenic function which brings about diabetes

7 Diabetes is always due to the same immediate factor, namely, a diminution of the insulogenic function and whether it is or is not associated with pituitary dysfunction, its course does not vary and the same treatment is indicated as in the ordinary case

THE MECHANISM OF INSULIN ACTION ¹

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The discovery and isolation of the physiologically effective principle of the internal secretion of the pancreas by Banting and Best ¹ in 1921 may be considered the culmination of the great amount of research work which received its impetus from the fundamental facts established by von Mehring and Minkowski in 1889 ². At that time it was first found that pancreatectomy in dogs resulted in complete diabetes. Thirty-two years of research on carbohydrate metabolism and the problem of diabetes mellitus prepared the way for the important findings of Banting and Best which resulted in the isolation of insulin and its application as a therapeutic agent. The work of von Mehring and Minkowski was the first contribution of value toward a solution of the question of the etiology of diabetes mellitus. Through the work of Banting and Best it is now known that the pancreas secretes a hormone which is essential to normal carbohydrate metabolism, which can be extracted from pancreatic tissues, and which is physiologically effective when administered parenterally. It has also been shown that insulin in the presence of extracts from certain body tissues, such as muscle and liver, aids in the fragmentation of the sugar molecule. Yet the actual mechanism of insulin action, the chemical structure of the hormone, and the reactions in which it plays such an important rôle are unknown. It is conceivable that if this mechanism were discovered the knowledge gained might prove a powerful illuminant in the still shrouded question of the etiology of diabetes mellitus. In other words, if we knew how insulin acts in reestablishing the diabetic body's potential toward a normal carbohydrate metabolism we might be able to discover the missing pathologic link between the picture as represented by a totally depancreatized dog and by a human being with severe diabetes.

I

The experimental and clinical work on the nature of insulin action reported in this article was suggested by the observation that the effect of insulin in the animal body differed materially according to the method

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1 Banting, F G, Best, C H, and MacLeod, J J R. *Am J Physiol* **62** 162 (Sept) 1922, *ibid* **62** 275, 1922, *Proc Am Physiol Soc*, 1925.

2 Von Mehring and Minkowski. *Centralbl f klin Med*, 1889, p 339, *Arch f exper Path u Pharmacol* **26** 371, 1899.

of administration³ If insulin is injected subcutaneously in healthy rabbits in quantities of 1 unit per kilogram of body weight the blood sugar is lowered after about one hour to about 50 per cent of the initial value This level is maintained over a period of from one to two hours The blood sugar then increases rapidly until at the fourth hour after the injection the normal level is again reached These observations were first made by Banting and Best and later by MacLeod and others

Insulin (1 unit per kilogram of body weight) administered *intradermally* in rabbits was found to have a greater blood sugar lowering effect than the same dose given subcutaneously to the same animal under identical conditions With intradermal administration the level reached at the second hour after the injection is usually lower and remains low up to the fourth hour, and at the sixth hour the blood sugar level is still below the initial value The same difference in reaction occurs when the insulin is used in the concentration of one-half unit per kilogram of body weight (Chart 1)

II

In the animal tests the difference between the two methods of administration consists of a more prolonged effect of the intradermally injected insulin The difference in time of absorption of the injected insulin in different body tissues cannot be used as an explanation of the prolonged effect observed in these experiments This is confirmed by the results in human beings, especially in diabetic patients, in whom the intradermal injection with definitely prolonged absorption of the insulin depot and the definitely later entrance of the insulin into the circulation is followed by a more rapid and more intensive effect This more rapid and greater effect of the intradermally administered insulin in human beings was demonstrated by shortening the observation intervals used in the animal experiments to one hour and, in six cases, to twenty minutes

Two experiments on the same subject, in which like doses of insulin from the same ampule and under the same dietary conditions were employed but in which the mode of administration of the insulin differed, constitute a series and are so referred to in the comment It is shown that in 86 per cent of the hourly series the intradermal injection is more effective at the first hour following the injection than the subcutaneous injection In the twenty minute series there is a definite effect at the first interval (twenty minutes) following the injection made intradermally and none at this interval following the subcutaneous injection, as shown in the composite curve of six series (Chart 2) The more rapid onset of the blood sugar lowering effect

³ Muller, E F, and Corbitt, H B J Lab & Clin Med 9 608 (June) 1924, 10 695 (June) 1925

of the intradermal injection cannot be due to a quicker absorption and entrance of the hormone into the circulation, as in that case the effect should disappear sooner than the effect following a subcutaneous injection, whereas the opposite is the fact. At the fourth hour 67 per cent of the intradermal injections had a greater blood sugar lowering effect than the subcutaneously introduced insulin under the same conditions and on the same subjects.

III

Since attempted intradermal injections of insulin in the human being were reported to be followed by necrosis of the skin we investigated the nature of the histologic changes in the skin and subdermal tissues following the intradermal and subcutaneous injections of insulin in animal experiments. The results showed that edema occurs in the area of the injection and that the vessel walls in this area show degenerative changes. The walls were found to be partially destroyed, thrombi were

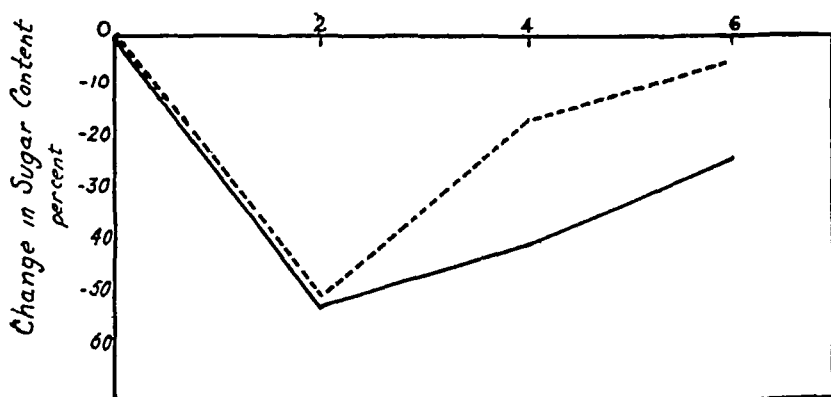


Chart 1—Comparative effects of intradermal and subcutaneous injections of insulin in rabbits in twenty-one experiments, solid line intradermal injections, eleven experiments, broken line subcutaneous injections, ten experiments

present, some of which completely closed the vessels, others only partly blocked them. A certain amount of round cell infiltration was found. However, these changes in the injected area concern so small a region that the reported necrosis could not have been due to them.⁴

Tests on human beings have shown that the intradermal injection of commercial insulin has no deleterious effect on the skin. In the course of the experiments about 100 intradermal injections of insulin (Insulin-Lilly) have been administered to nondiabetic as well as to diabetic patients. In no case was the slightest reaction or damage to the skin noticed, either immediately or later, with the exception of slight and probably temporary pigmentation that was observed at the site of the

⁴ Muller, E. F., and Myers, C. N. *Proc Soc Exper Biol & Med* **22** 92 1924

injection One patient, a girl, aged 12 years, with severe diabetes mellitus, was treated under our direction while in the Roosevelt Hospital (courtesy of Dr Evan M Evans) Over a period of twenty-two days she was given forty-four intradermal injections of insulin, from one to three injections daily, the average daily dose amounting to 28 units As

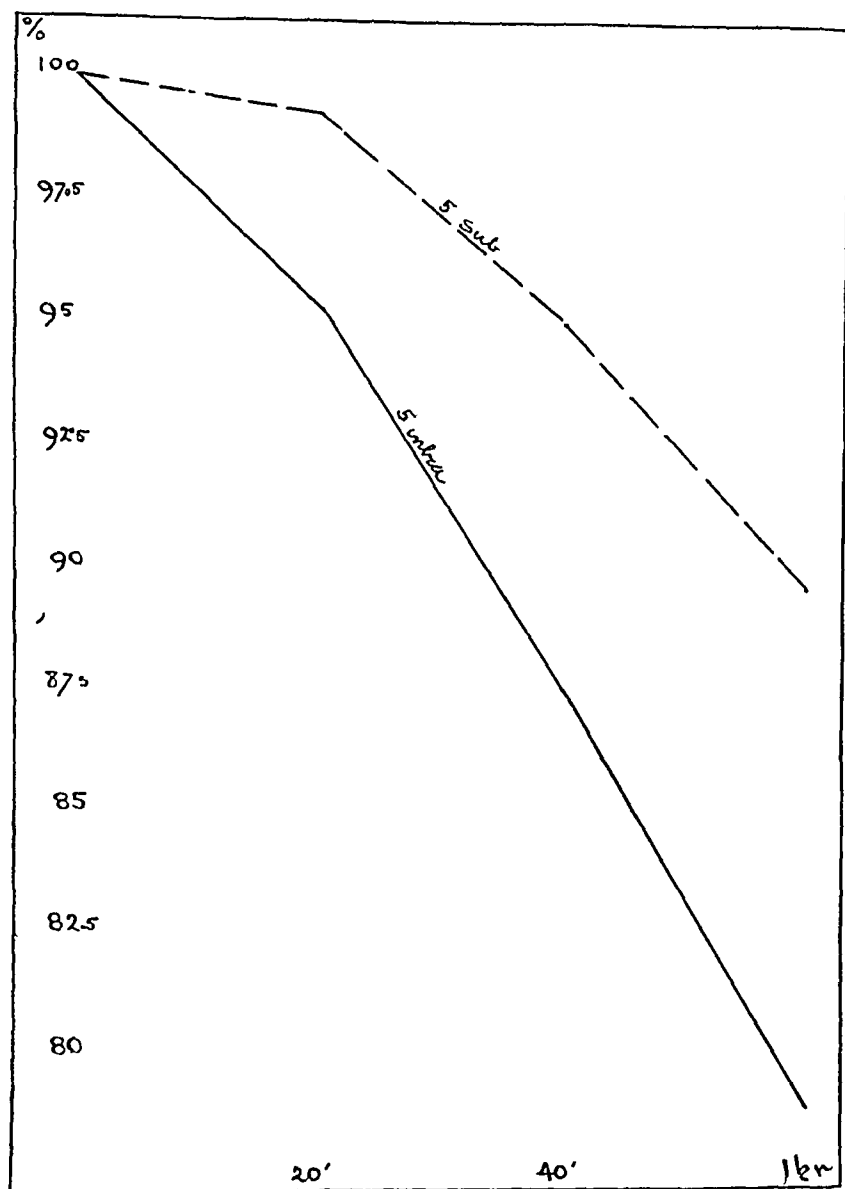


Chart 2—Composite curves of six series showing effect on blood sugar level of subcutaneous and intradermal insulin injections (Table 3)

much as 14 units of the U-40 strength (0.35 cc) was readily administered in a single wheal. Extensor surfaces of the forearms and thighs were used. Six weeks after the date of the last intradermal injection a few faintly pigmented spots were to be found on the forearms at the sites of some of the intradermal injections.

In all the tests the same lot number of insulin of the U-40 strength was used and insulin from the same ampule was employed for the various tests on the same individual. From 5 to 20 units could be administered intradermally in from one to three wheals. The procedure was as follows: A small fold of the skin of the extensor surface of the forearm was raised without pressure, cleansed with alcohol and a hypodermic needle introduced into the skin parallel to the surface. The needle and syringe must be washed with distilled water followed by dry sterilization. Any other method, especially sterilization by boiling in tap water must be avoided. If the wheal is administered correctly a white elevation remains visible for about ten minutes, after this the

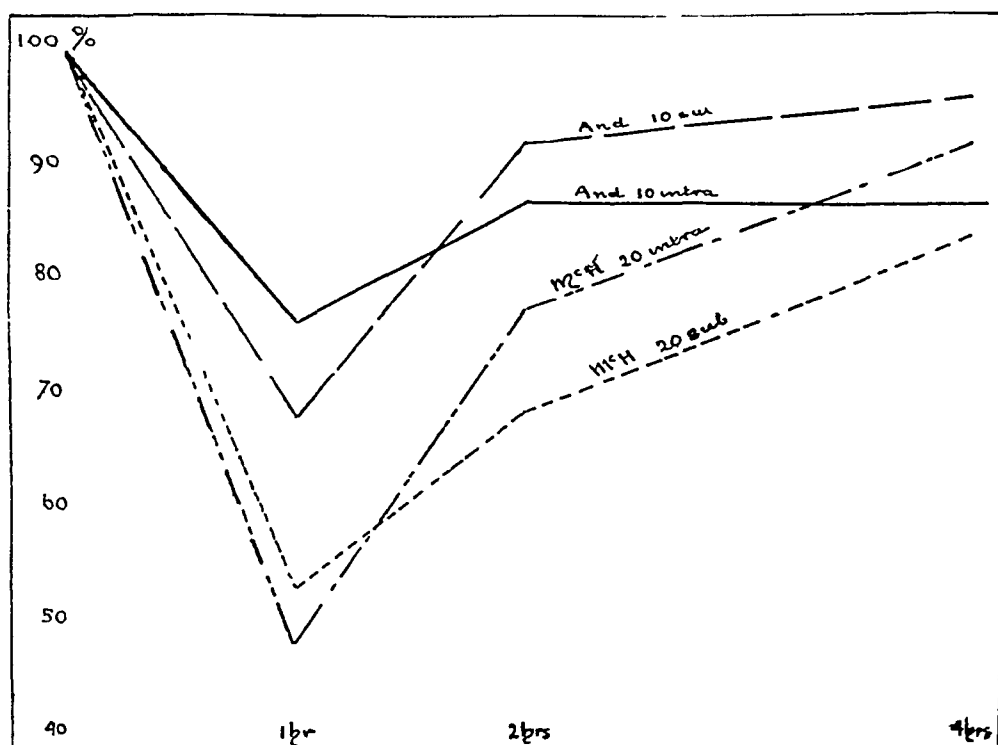


Chart 3—Effect on blood sugar level in nondiabetic patients of subcutaneous and intradermal insulin injections

margins become red and slight edema occurs in the surrounding area, but the center remains quite white for about fifty minutes. Later, the entire wheal again becomes white. The area of the wheal increased markedly in a large number of cases but remained sharply distinguished from the surrounding tissues. In hypersensitive cases the wheal at the later stage is not sharply distinguished from the other skin but is twice as large as the first visible wheal, and its white center and red margins remain visible for hours. In a few cases this increase in size does not take place but the wheal remains visible for from three to four hours thus differing from a wheal induced by injection of a nonspecific protein.

Through the strong counterpressure of the skin small amounts of insulin may occasionally escape from the wheal after the needle is withdrawn. Experiments in which this occurred or in which slight bleeding occurred have been excluded.

Proof of a proper intradermal technic consists in (1) the evidence of a strong counterpressure against the advancing piston of the syringe, and (2) the immediate appearance of depressions of the hair follicles. In a few cases a slight pigmentation at the site of the injection was noticed subsequently but in no case was necrosis or clinical inflammation observed.

IV

Irrespective of the condition of the subject or of his carbohydrate metabolism at the time, it has been shown that under conditions as nearly constant as possible the two methods of administration differ in their effect on the blood sugar level. The blood sugar level of a non-diabetic subject in a morning fasting condition does not change materially during an observation period of from four to six hours. If one injects a nondiabetic subject with insulin the difference in the blood sugar lowering effect between the intradermal and the subcutaneous injection is small and not uniform. However, one feature in common is the quick recovery to the normal blood sugar level, even when large doses of insulin are used (Chart 3). The difference in response to the two methods at the first hour is slight, except for the smallest dose. The deepest point of the blood sugar curve is obtained during the first hour after both methods of injection. Rapid recovery to normal follows this first blood sugar lowering effect. In these tests the difference between intradermal and subcutaneous injections is greater with small amounts of insulin (5 units). This was also found to be the case when healthy animals were used in similar experiments. The effect of the intradermal injections in human beings with normal carbohydrate metabolism is more prolonged after the injection of small doses. With larger doses the subcutaneous injection has the more prolonged effect.

V

In patients with diabetes mellitus of varying degrees of severity the difference in reaction of the blood sugar level to the two methods of administration is more marked than in nondiabetic subjects (Table 2). However, this difference as between one case and another was not found to be a measure of the clinical severity of the disease. In other words, a clinically mild case might show a greater difference in the blood sugar level at one hour following the two methods of administration than a case clinically of greater severity. One feature of the curve did, however, run parallel to the clinical severity of the cases examined, namely,

the rapidity of the return of the blood sugar toward its original level. It is possible, however, that the difference in the reaction of the individual patient with diabetes mellitus to the two methods of administration may prove a new basis for a revised clinical classification of the disease. A study of the reaction of the individual case to such tests might conceivably have a bearing on prognosis and treatment.

For purposes of discussion we have divided the clinical material used in these tests into four groups, all showing glucosuria, as follows:

A *Very Mild Glycosuria (Diabetes?)*—In this group were three cases (Cases 1, 2 and 3) of glycosuria without other symptoms of diabetes mellitus, the patients were men, aged 43, 50 and 54. The

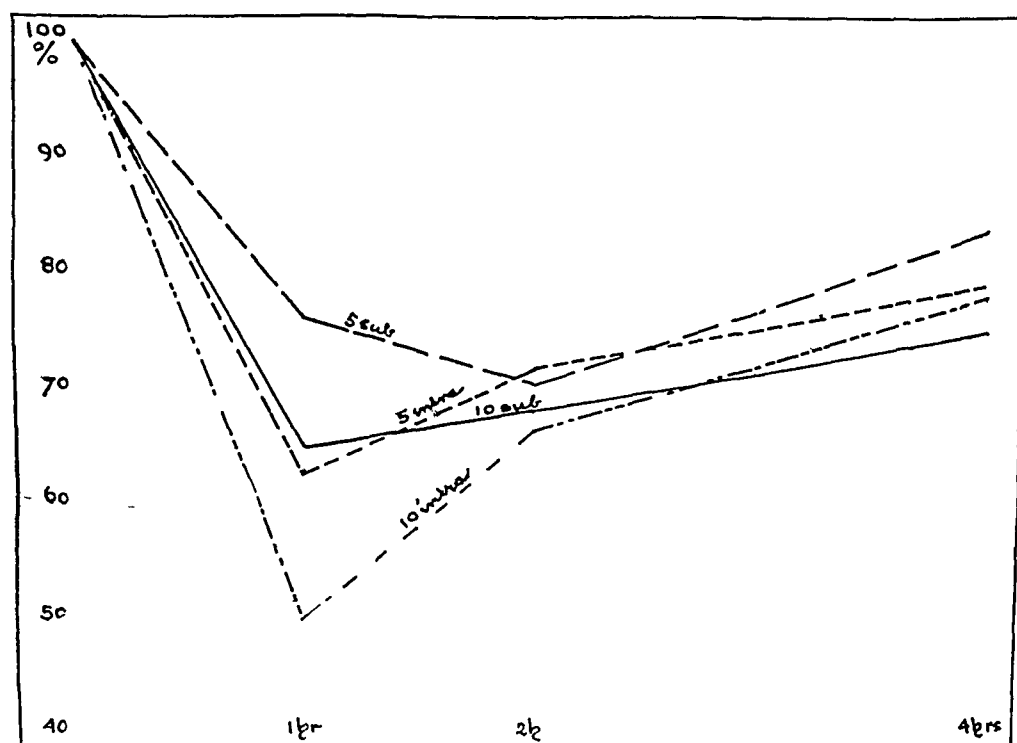


Chart 4—Effect on blood sugar level in a case of mild glycosuria of subcutaneous and intradermal insulin injections

original blood sugars were 182, 123 and 129 mg per cent, respectively. The tests in these cases all followed a similar course and are represented by the curve of Patient 3 (Chart 4). It may be seen that there is a sharp recovery toward the normal level of the blood sugar with the intradermal administration following the drop registered in the first hour. The decline in the blood sugar after the subcutaneous injection continues into the second hour, showing a more prolonged but not as strong a hypoglycemic effect as the intradermal injection. At the first hour the average blood sugar lowering effect in these three cases for the 5 unit doses was 80 per cent of the initial blood sugar following

the subcutaneous injection and 60 per cent of the initial blood sugar for the intradermal injection. The 10 unit doses showed a similar relationship.

B Mild Diabetes Mellitus—In this group were three cases. Patient 4, a woman, aged 39, had an original blood sugar of 195 mg per cent and 1.5 per cent sugar in the urine. Glycosuria had been first found thirteen months previously, she had pruritus and polyuria. Patient 6, a woman, aged 43, had an original blood sugar of 260 mg per cent and urine sugar 1 per cent. Glycosuria had been first found four months previously, she had pruritus and had lost weight. Patient 5, a man, aged 65, had an original blood sugar of 204 mg per cent and urine sugar 1 per cent. The sugar had been first discovered fourteen years previously, he had furunculosis, polyuria and polydipsia, and had lost weight. The urines were sugar-free on an average total available intake of 85 Gm of carbohydrate and 60 Gm of protein. In this group of cases there was also a definite similarity of architecture in the curves resulting from the tests. The curve of Case 5 is typical (Chart 5).

C Moderately Severe Diabetes Mellitus (Insulin Treatment)—In this group were six cases. Patient 11, a woman, aged 22, had an original blood sugar of 240 mg per cent and urine sugar of 1.6 per cent. Glycosuria had been first discovered two years and nine months previously, she had pruritus, had lost weight and suffered from nervousness and weakness. The urine was sugar-free on 38 Gm of carbohydrate, 61 Gm of protein and 175 Gm of fat. Carbohydrate tolerance was sensitive to slight infections and nervous and emotional strains. Insulin treatment had been started twelve months previously, and the dose had been increased from 5 units twice a day to 10 units twice a day.

Patient 12, a colored man, aged 31, had an original blood sugar of 350 mg per cent and urine sugar 2 per cent. Glycosuria had been first discovered fourteen months previously, he had polyuria and polydipsia, had lost weight and suffered from weakness. He developed pulmonary tuberculosis while under observation. The urine was sugar-free before the tuberculous infection on 108 Gm of carbohydrate, 40 Gm of protein and 204 Gm of fat, after the tuberculous infection on 40 Gm of carbohydrate, 54 Gm of protein and 185 Gm of fat. Insulin treatment was begun at the time of the tests, the dose being 10 units twice a day.

Patient 10, a colored man, aged 43, had an original blood sugar of 278 mg per cent and urine sugar 4 per cent. Glycosuria had been first discovered six months previously, he had moderate polyuria and polydipsia, and had lost weight. The Wassermann reaction was ++++ (asymptomatic ? syphilis). The urine was never sugar-free without insulin. The patient was known to make untruthful reports as to his food intake. The insulin treatment had been started two months previously, the dose being 10 units twice a day.

Patient 8, a woman, aged 46, had an original blood sugar of 333 mg per cent and urine sugar 8.5 per cent. Glycosuria had been first discovered ten months previously, she had polyuria and polydipsia, had lost weight, and had chronic osteomyelitis of the phalanx of the thumb. The urine was sugar-free on 20 Gm of carbohydrate, 50 Gm of protein and 190 Gm of fat. Insulin had been started seven months previously, the dose being 12 units twice a day.

Patient 7, a man, aged 50, had an original blood sugar of 250 mg per cent and urine sugar 1.43 per cent. Glycosuria had been first dis-

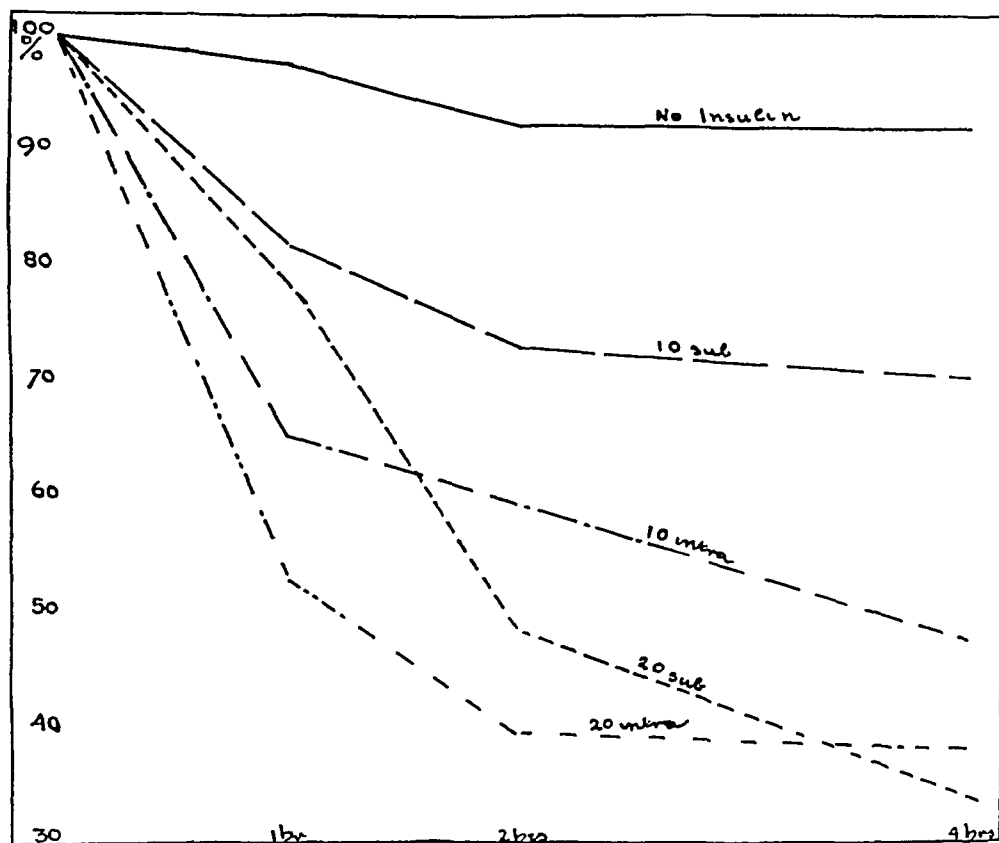


Chart 5—Effect on blood sugar level in a case of mild diabetes of subcutaneous and intradermal insulin injections

covered six years and eleven months previously, he had polyuria, polydipsia and polyphagia, he had lost weight and had a slight blurring of vision. The urine was sugar-free on 30 Gm of carbohydrate, 50 Gm of protein and 250 Gm of fat. Insulin had been started fourteen months previously, the dose being 10 units twice a day. The patient was of the neurotic, emotional type.

Patient 9, a man, aged 55, had an original blood sugar of 666 mg per cent and urine sugar 4 per cent (155 Gm). Glycosuria had been first discovered one and a half years previously, he had polyuria, polydipsia and polyphagia, he had lost weight and suffered from weakness

He was put on insulin treatment at the time the tests were started, 20 units twice a day was increased to 30 units twice a day and then after one month progressively decreased until he was receiving none five months after the beginning of the treatment. He was on a diet of 80 Gm of carbohydrate, 80 Gm of protein and 140 Gm of fat. Five and one-half months after the beginning of the insulin treatment the urine was sugar-free on a diet of 120 Gm of carbohydrate, 80 Gm of protein and 150 Gm of fat and no insulin. He gained 13 pounds (5.9 Kg) in weight and is working. The fasting blood sugar is 160 mg per cent. The gradual decrease in this patient's fasting blood sugar level under insulin treatment and his increase in tolerance is striking (Table 1).

The tests in this group show a still more prolonged blood sugar lowering effect of the insulin by both methods of administration. The difference in the effect on the blood sugar level between the two methods is on the average most marked at the second and fourth hour. The greatest difference in the blood sugar lowering effect between the two methods of administration occurs at a later period after injection than

TABLE 1—Results of Insulin Treatment in Case 9

	Dates						
	Nov 18	Nov 28	Dec 5	Dec 12	Dec 19	Jan 14	Jan 28
Fasting blood sugar in mg per cent	666	500	450	360	204	180	160
Urine sugar at time of blood sugar, per cent	18	26	25	22	0	0	0

in the previously described group. On the other hand, there is a greater variation in the degrees of difference in the effect of the two methods at the first hour when the individual curves in this group of cases are compared. The curve for Case 11 (Chart 6) has been chosen as the most typical for this group. Twenty minute tests carried out in three of these cases showed conclusively that the intradermal injection results in an earlier onset as well as in a greater hypoglycemic effect.

D Severe Diabetes Mellitus (Insulin Treatment)—There were three cases in this group.

Patient 13, a woman, aged 16, had an original blood sugar of 364 mg per cent and urine sugar 2 per cent. Glycosuria had been first discovered twenty months previously, the patient was sugar-free only on starvation. Insulin treatment was started nineteen months previously. The dose previous to the tests was 15 units twice a day. The symptoms were amenorrhea (menses had begun at 13½ years and were regular up to one month before sugar was discovered) and marked depression of tolerance secondary to any slight infection and to nervous and emotional strains.

Patient 15, a woman, aged 26, had an original blood sugar of 364 mg per cent and urine sugar 1.6 per cent. Glycosuria had been first discovered four years and eight months previously following a toxemia of pregnancy, she had polyuria and polydipsia, had lost weight and was sugar-free on starvation only. Insulin treatment had been started eighteen months before examination, the dose being 10 units twice a day. This was gradually increased to 30 units twice a day. She went through a second pregnancy, stillbirth resulting. The insulin dose was now 20 units three times daily. The patient was of an emotional, neurotic

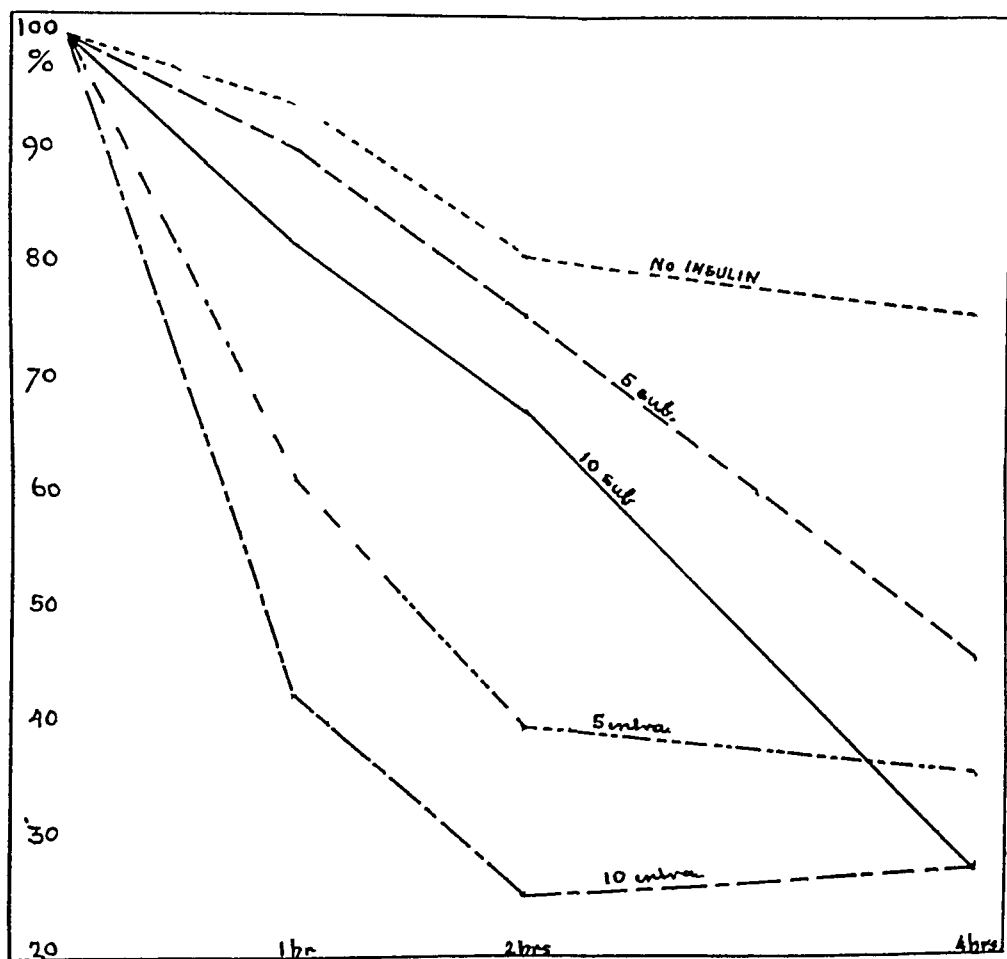


Chart 6—Effect on blood sugar level in a case of moderately severe diabetes of subcutaneous and intradermal insulin injections

type. The depression of the tolerance was marked following slight infections and emotional strains.

Patient 14, a woman, aged 41, had an original blood sugar of 243 mg per cent and urine sugar 2.9 per cent. Glycosuria had been first discovered three years and ten months previously, she had moderate polyuria, polydipsia, polyphagia and pruritus, she had lost weight and was sugar-free on starvation only. Insulin treatment had been started

eighteen months before examination, 20 units three times daily. The patient was of phlegmatic type.

The reaction to the insulin injections in this group differs from the curves previously discussed in that the first hour effect of the intradermal dose is slight if not actually reversed, i. e., an increase in blood sugar level. During the second hour the drop is slight, and becomes pronounced only in the last period. The subcutaneous injection results in a slightly greater drop in the blood sugar level at the first hour, a more pronounced effect at the second hour and the level reached at the fourth hour is still below that reached following an intradermal injection of like

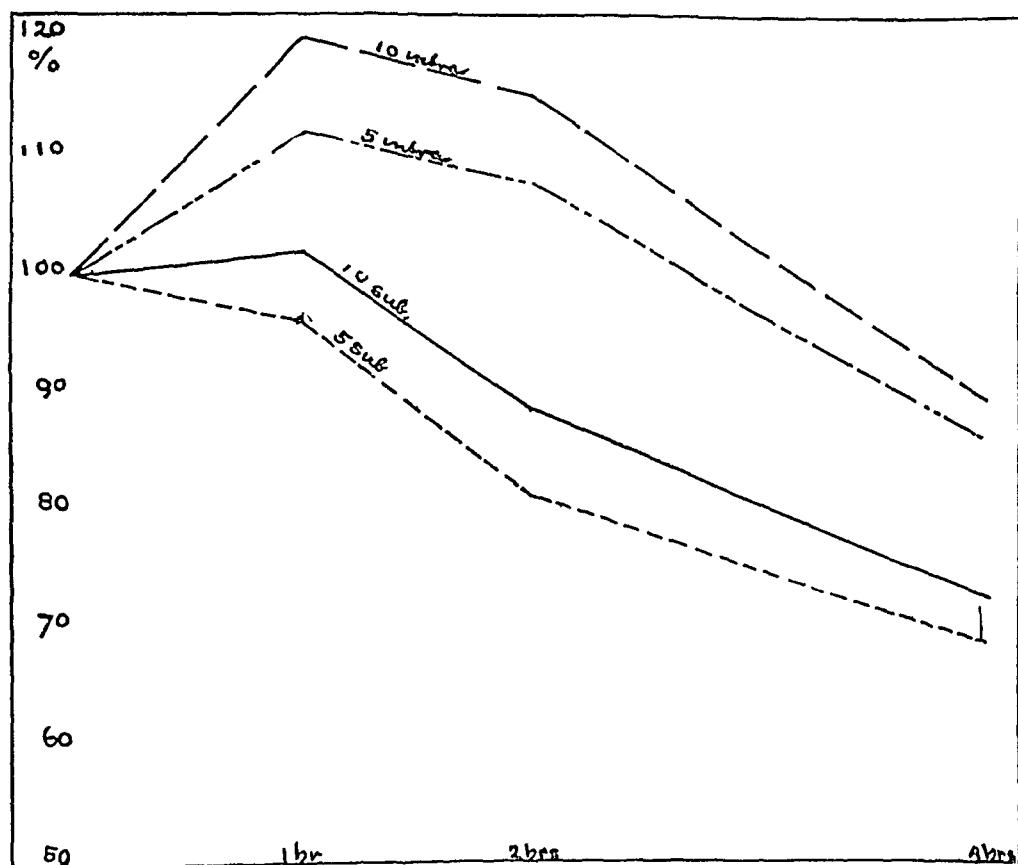


Chart 7—Effect on blood sugar level in a case of severe diabetes of subcutaneous and intradermal insulin injections

dosage. The curves obtained in the tests on Patient 14 are shown in Chart 7. The subcutaneous injections of from 5 and 10 units had practically no effect on the blood sugar level at the first hour, but a decided effect at the second and the fourth hour. The intradermal injections of like doses were followed by a decided rise in the blood sugar level at the first hour, a negligible drop from that level at the second hour, and a decided drop, reaching 12 and 14 per cent below the initial blood sugar level, at the fourth hour. The depression in the blood sugar level obtained by the subcutaneous doses was not reached,

TABLE 2—*Blood Sugar Following Intradermal and Subcutaneous Insulin Injections in Diabetes Mellitus*

Case	Insulin		Blood Sugar Before Insulin, Mg per Cent	Blood Sugar Following Injection in Percentage of Initial Value			Sugar Excretion in Urine, Gm		Food	
	Units	How Given		1 Hour	2 Hours	4 Hours	Before	After Insulin	Min utes After	Total Available Carbo hydrate
1	5	Intradermally	156	55	63	65	0	0	85	32
	5	Subcutaneously	123	72	69	76	0	0	113	32
	10	Intradermally	168	48	53	61	0	0	120	132
	10	Subcutaneously	208	56	35	50	0	0	85	276
2	5	Intradermally	114	74	79	97	Trace	0	Fasting	
	5	Subcutaneously	129	89	84	84	Trace	0	Fasting	
3	5	Intradermally	118	64	72	79	Trace	0	105	290
	5	Subcutaneously	111	77	71	84	Trace	0	110	290
	10	Intradermally	108	51	67	78	Trace	0	120	290
	10	Subcutaneously	114	65	69	75	Trace	0	110	290
4	10	Intradermally	175	91	73	63	Trace	0	Fasting	
	10	Subcutaneously	196	93	80	76	Trace	0	Fasting	
5	10	Intradermally	222	66	60	48	0.23	0.86	80	450
	10	Subcutaneously	282	81	74	71	No specimen obtained		115	500
	20	Intradermally	298	53	40	38	0.95	1.37	130	407
	20	Subcutaneously	250	80	50	35	0.23	0.67	Fasting	
	No insulin		256	98	93	93	0.46	1.11	145	450
6	10	Intradermally	260	50	34	39	0.56	0	Fasting	
	10	Subcutaneously	210	90	58	43	0	0	Fasting	
7	5	Intradermally	408	82	73	58	1.98	4.89	108	317
	5	Subcutaneously	385	84	68	65	3.60	7.68	70	317
	10	Intradermally	371	63	48	49	1.53	0.52	90	384
	10	Subcutaneously	400	87	71	40	3.15	2.67	80	456
	No insulin		348	96	94	94	1.82	4.33	115	400
8	5	Intradermally	340	91	80	67	1.50	4.40	120	178
	5	Subcutaneously	270	106	86	74	0.96	3.39	120	83
	10	Intradermally	352	86	74	54	2.08	4.76	120	178
	10	Subcutaneously	377	96	83	69	2.68	5.58	120	236
	No insulin		346	98	93	74	2.28	5.37	120	101
9	5	Intradermally	666	88	86	62	3.37	5.52	170	144
	5	Subcutaneously	500	100	93	67	2.11	11.65	Fasting	
	10	Intradermally	450	78	69	57	4.90	7.55	Fasting	
	10	Subcutaneously	360	84	65	46	3.74	4.41	Fasting	
	10	Intradermally	204	75	65	52	0	0	Fasting	
	5	Intradermally	180	74	66	53	0	0	Fasting	
	5	Intradermally	200	77	69	60	0	0	Fasting (epinephrin)	
	5	Subcutaneously	160	81	68	54	0	0	Fasting (epinephrin)	
10	5	Intradermally	377	88	75	56	0.95	1.60	80	384
	5	Subcutaneously	286	85	80	64	0.33	1.04	60	284
	10	Intradermally	235	68	34	29	0.04	0.11	60	219
	10	Subcutaneously	274	72	74	49	0.08	0.35	95	219
11	5	Intradermally	317	60	40	36	3.90	1.15	110	257
	5	Subcutaneously	256	90	76	46	0.17	0.12	Fasting	
	10	Intradermally	308	43	26	28	3.50	0.34	120	313
	10	Subcutaneously	298	82	68	28	4.30	1.75	120	313
	No insulin		364	94	81	76	7.16	3.47	150	479
12	5	Intradermally	190	88	68	43	0	0	67	209
	5	Subcutaneously	177	97	87	68	0	0	75	236
	10	Intradermally	250	84	74	40	0.81	0.88	Not fasting	
	10	Subcutaneously	250	118	76	67	No specimen obtained		Not fasting	
	20	Intradermally	307	93	65	41	1.00	1.51	Not fasting	
	20	Subcutaneously	286	96	84	67	1.31	1.65	Not fasting	
	No insulin		400	95	91	96	2.45	10.50	60	414
13	5	Intradermally	364	86	82	67	3.22	2.22	Fasting	
	5	Subcutaneously	400	90	78	68	5.08	6.04	Fasting	
14	5	Intradermally	385	112	108	86	2.10	13.64	75	210
	5	Subcutaneously	434	96	81	69	2.87	12.00	105	258
	10	Intradermally	346	120	115	83	0.29	0.34	Fasting	
	10	Subcutaneously	345	102	88	73	1.13	2.59	Fasting	
	10	Intradermally	244	87	100	90	Trace	0.28	Fasting	
15	10	Subcutaneously	358	100	79	62	5.32	1.36	120	200

however One set of these curves was run with the patient in a fasting condition while the other set was run following a meal of 22 Gm of total available carbohydrate, taken ninety minutes before The increase following the intradermal injection cannot be attributed solely to resorption from the gastro-intestinal tract for the rise in blood sugar occurred also in the fasting condition

VI

The original blood sugar figures from which these curves were obtained, as well as the figures of the other cases, will be found in Table 2 The blood sugar determinations preceding the insulin injections are given in absolute numbers, i e., milligrams per cent The determinations at later time intervals are given in percentage of this initial value for the purpose of comparison

TABLE 3—*Blood Sugar Levels Following Intradermal and Subcutaneous Injections of Five Units of Insulin U-40*

Case	Blood Sugar Following Intradermal Injection				Blood Sugar Following Subcutaneous Injection				Food
	Mg per Cent Before Injection	Percentage of Initial Value			Mg per Cent Before Injection	Percentage of Initial Value			
		20	40	60		20	40	60	
		Minutes After	Minutes After	Minutes After		Minutes After	Minutes After	Minutes After	
11	210	95	86	76					Fasting
12	215	97	90	88	237	101	101	94	Fasting
16	185	97	93	84	244	99	95	94	Fasting
7	304	95	93	90	318	105	100	90	Black coffee
9	158	96	79	58	177	95	88	83	Fasting
5	182	93	84	78	192	96	91	87	Fasting
Average		95.5	87.5	79.0		99.2	95.0	89.6	
Average drop in percentage		4.5	12.5	21.0		0.8	5.0	10.4	
Per unit		0.9	2.5	4.2		0.16	1.0	2.1	

In a number of cases the blood sugar level was determined at the same intervals but without the insulin injection In six additional series of one hour only, the blood sugars were determined at twenty minute intervals following the injections and these determinations are given in Table 3

From the twenty minute series (Chart 2) it is apparent that there is a blood sugar lowering effect of intradermally injected insulin before an effective amount of the hormone can possibly be present in the blood stream for the subcutaneously administered equal dose of insulin shows no such effect twenty minutes after the injection From the observations reported in the foregoing it is concluded that insulin injected intradermally must have an initial specific action produced in some way other than through the usual contact of the hormone with the tissue fluids and cells

Summarizing the four hour experiments given in Table 2, it is shown that twenty-nine, that is, 86 per cent of the thirty-three four

hour series, show a greater reduction in the blood sugar level at the first hour following the intradermal injection than at the first hour following the subcutaneous injection of an equal dose. At the second hour, twenty-three (70 per cent) of the intradermal injections resulted in a lower blood sugar level than did the subcutaneous injections. At

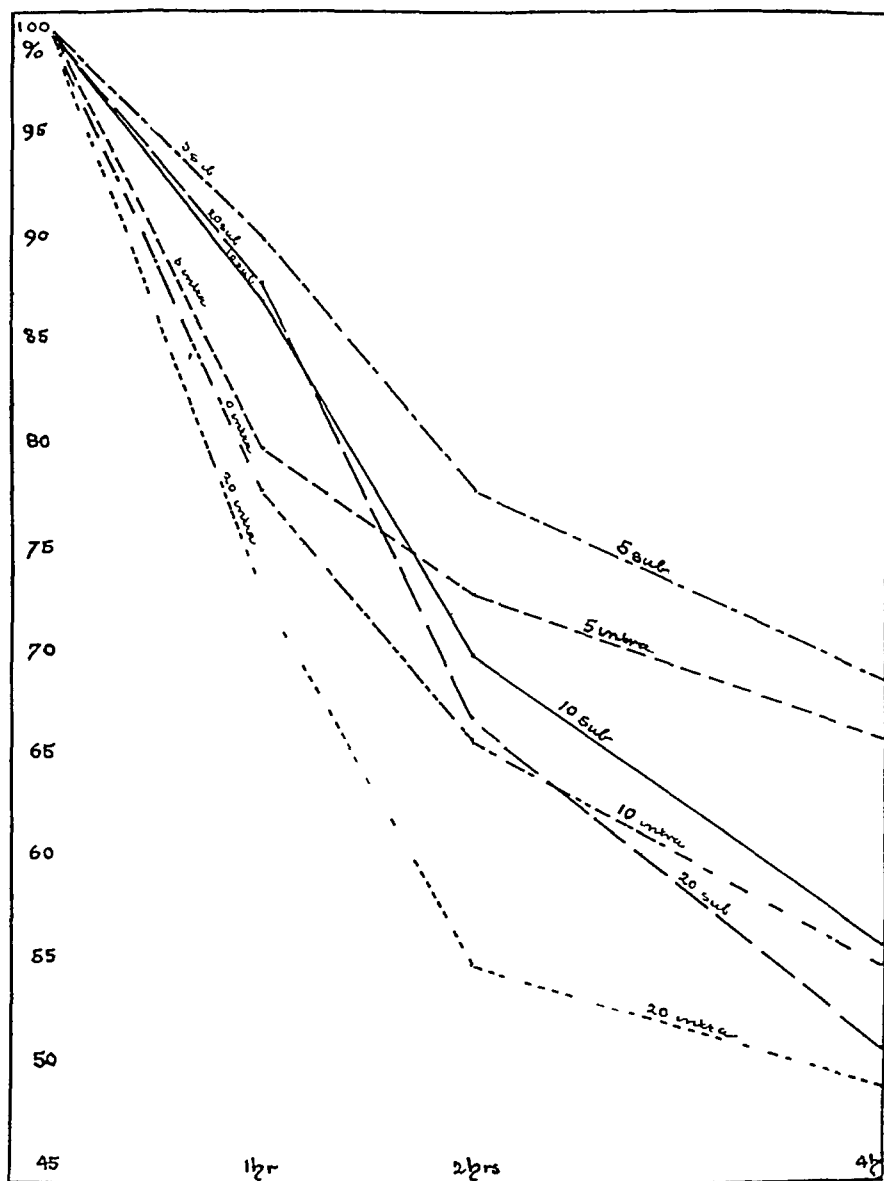


Chart 8—Composite curves of thirty-three series showing effect on blood sugar level of subcutaneous and intradermal insulin injections (Table 2)

the fourth hour, twenty (67 per cent) of the series showed a greater hypoglycemia with intradermal administration.

The difference in the response to the two methods of administration as manifested by the hypoglycemic effect is most striking with the smallest doses (i.e., 5 units) and at the first hour after the injection.

Chart 8 gives the composite curves of all the 5 and 10 unit series. The fact that the maximum difference falls at the first hour and the gradual decrease in this difference at the subsequent time intervals is shown in this curve.

When we compare typical curves of the various groups, the greater hypoglycemic effect of the insulin injected intradermally as compared to the effect of a like dose given subcutaneously may be noted in all groups except in the severe cases. This difference in effect occurs at the first hour following the injection, and decreases in the mild cases after the first hour. The difference in effect is progressively extended to the later intervals of the experiments with the increase in severity of the disease. In the severe cases the difference at the first hour is absent or reversed, and the subcutaneous injection results in a greater blood sugar lowering effect which persists throughout the period of the experiment.

In the normal there is little difference if any between the hypoglycemic effect of insulin administered intradermally and that of a like dose given subcutaneously. Probably the defense mechanism of the body to the insulin, especially glycogenolysis, is initiated at an early stage and cuts down the greater hypoglycemic effect of the intradermally administered dose. This mechanism also causes the recovery toward the original blood sugar level to be well under way at the second hour following the injection. In mild diabetes this mechanism manifests itself at the second hour following an intradermal injection though to a smaller degree, while for the subcutaneously administered dose the hypoglycemic effect of insulin extends into the second hour and recovery toward the original level begins in the last period. The onset of glycogenolysis is not determined solely by the extent of the hypoglycemic effect, the intensity of the stimulus due to the insulin injection also is a factor. In the majority of cases the recovery toward the original level starts from a slightly lower blood sugar level following subcutaneous injection than following an intradermal injection. The nearer to normal the condition of cell metabolism, the more quickly will the cells receive and react to glycolytic stimuli due to the presence of the hormone, or to glycogenolytic stimuli due to the abnormally low blood sugar level. In the severe diabetic case glycolytic activity as well as glycogenetic activity is greatly impaired or absent. The first effect of the intradermal injection may result in an increase in the blood sugar due to glucogenic activity of the cells.

The reaction of the individual to either subcutaneous or intradermal insulin administration would seem to depend in its degree on (1) the condition of carbohydrate metabolism at the time, (2) the reactivity of the nervous system to chemical stimuli, (3) the amount of glycogen storage in the liver and in the muscles, and (4) the rate of resorption of injected insulin into the circulation.

Insulin injected subcutaneously enters the blood stream and is brought to the tissues more promptly than when the same dose is given between the layers of the skin Kasahara⁵ showed that the resorption of true solutions, colloidal solutions and cell and bacterial suspensions when introduced intradermally is materially delayed as compared to identical injections administered subcutaneously If the increased response to an intradermal injection at the first hour following the injection were due to a quicker resorption and entrance in greater quantity of the hormone into the blood stream, increasing the dose should result in an even greater difference in the lowering of the blood sugar between the two modes of injection However, the reverse is the fact The results cannot therefore be explained by a quicker and more complete resorption of the intradermally introduced insulin

The blood sugar decrease must always be preceded by a biologic insulin action If the decrease is observed within twenty minutes after the injection the insulin action must have taken place before the end of this period There is no possibility of establishing a relationship between a postponed resorption and a more rapid effect, if the activity of the insulin is dependent on the presence of the hormone in the circulation In 86 per cent of the experiments the intradermal injection was followed by greater lowering of the blood sugar level at the first hour following the injection than the subcutaneous injection of like dosage under standard conditions This also cannot be explained by the delayed absorption if the activity of the insulin were dependent on the presence of the hormone in the circulation It is also to be considered that the pathway of absorption from the intradermal layers of the skin to the circulation is over a longer route and it may be postulated that in that case the loss by adsorption is greater and hence the amount of active material which reaches the circulation is less than when insulin is administered subcutaneously This loss by adsorption will be the greater the larger the dose The excretion in the urine and loss of active insulin in the circulation must be the same, no matter from what region the insulin has entered the circulatory system

The absorption from the subcutaneous area is more rapid and larger quantities of insulin are present in the circulation and in the tissues at a given time following the subcutaneous injection, and hence, a small dose will be exhausted more rapidly This is demonstrated by the relatively prolonged effect of small doses introduced intradermally When a small dose, i e., 5 units, is used the effect of the intradermal dose will outlast that of the subcutaneous With larger doses the loss by adsorption is relatively greater and the effect is comparatively prolonged Increasing the doses of insulin injected intradermally does not

result in a corresponding increase in effect, that is, a smaller dose has a greater per unit effect, as shown by the blood sugar determination, than the larger dose at the first hour following the injection. It may be concluded that the direct hormone action of insulin in the blood and tissues is not the only factor involved in its physiologic action. The evidence of the existence of another factor is supplied by the reaction to intradermal injection and, as has been shown, this factor must even be effective in the absence of the circulating hormone.

VII

If the hormone activity of the insulin consists of an effect on the sugar molecule, either by causing a molecular rearrangement to a more reactive form or by favoring the formation of a more reactive compound, such an activity should be observable in the blood *in vitro* by an increased glycolysis.

If the insulin in addition causes increased glycogenetic activity or storage within the cells in some other nonreducing form and thereby removes the glucose from the blood and the tissues, the glycolytic activity of the blood will not express this activity of the insulin.

Glycolytic activity tests were made for the purpose of determining if the glycolytic activity of the blood increases after insulin administration or not. A marked increase of the glycolytic activity after the administration of insulin may be attributed to the entrance of the hormone into the blood stream or tissues.

The glycolytic activity as it occurs in the blood, determined *in vitro*, indicates the glycolysis taking place *in vivo*. It may be taken as a certain measure of physiologic glycolysis only if the limitations inherent in the method are recognized.

In the living body conditions favor the reaction. Oxygen is constantly supplied, the p_H is maintained, the reaction products are removed, and the substrate is constantly replenished. None of these conditions is fulfilled *in vitro*. Furthermore, the effect of the anticoagulant must also be taken into account. The measurement of glycolytic activity of the blood must be carried out under standard conditions in order to minimize the experimental error. The temperature is a factor and the erythrocytes must be morphologically intact in order that glycolytic activity may proceed. The glycolytic activity determined at half-hour intervals was found to proceed in almost linear progression up to two and a half hours. A two hour incubation period was therefore chosen as one most likely to give distinct difference in the blood sugar. The anticoagulant was used in constant proportion. The blood was drawn and divided into aliquot parts, one of which was immediately precipitated while the other, carefully stoppered, was kept in the incubator at

body temperature for two hours. At the end of the incubation period the water dilution was added and the proteins precipitated. The time allowed for the precipitation of the proteins and for the filtration, as well as the size and the thickness of the filter paper, were carefully standardized. Table 4 gives the results of the individual experiments. In Chart 9 the average blood sugar levels following intradermal and subcutaneous insulin injections as well as the glycolytic activities of these bloods are shown. The blood sugar level as well as the glycolytic activity are expressed in percentage of the initial value, i. e., the value preceding the injection.

TABLE 4—*Glycolysis Following Intradermal and Subcutaneous Insulin Injections*

Case	Initial Blood Sugar Concentration, Mg per Cent	Insulin		Two Hours Glycolysis in Mg per Cent of Absolute Value of Blood Sugar, Time After Injection				Two Hours Glycolysis in Percentage of Initial Glycolysis, Time After Injection			Time After Injection of Lowest Blood Sugar, Hrs	Food, If Any	
				Before	1 Hr	2 Hrs	4 Hrs	1 Hr	2 Hrs	4 Mrs		Min utes After	Total Avail able Car bohy- drate
		Unit	How Given										
13	364	5	Intradermally	13	13	25	34	100	192	261	4	Fasting	
	400	5	Subcutaneously	10	29	23	24	290	230	240	4	Fasting	
1	156	5	Intradermally	17	14	20	7	82	118	41	1	83	3 2
	123	5	Subcutaneously	20	15	18	14	75	90	70	2	113	3 2
	168	10	Intradermally	17	25	34	17	147	200	100	1	120	13 2
	208	10	Subcutaneously	8	12	33	13	150	412	162	2	85	27 6
7	371	10	Intradermally	19	14	9	5	74	47	26	2	90	38 6
	400	10	Subcutaneously	22	16	32	22	73	145	100	4	80	45 6
9	450	10	Intradermally	23	15	17	22	65	74	99	4	Fasting	
	360	10	Subcutaneously	17	29	13	22	170	77	129	4	Fasting	
	204	10	Intradermally	17	16	18	22	94	106	129	4	Fasting	
17	140	10	Intradermally	45	29	52	25	64	116	56	1	60	48 8
	98	10	Subcutaneously	22	27	21	17	123	96	78	4	155	35 5
	109	5	Intradermally	19	12	8	8	63	42	42	1	155	53 7
	105	5	Subcutaneously	23	30	27	9	131	118	39	1	130	53 7
11	317	5	Intradermally	23	23	33	13	100	144	57	4	110	25 7
	256	5	Subcutaneously	15	13	16	6	67	107	40	4	Fasting	
6	208	10	Intradermally	31	24	22	16	78	71	52	4	Fasting	
	220	10	Subcutaneously	24	27	22	12	113	92	50	4	Fasting	
3	118	5	Intradermally	18	7	12	7	39	67	39	1	105	29 0
	111	5	Subcutaneously	17	18	20	17	106	118	100	2	110	29 0
	108	10	Intradermally	23	20	22	24	87	96	105	1	120	29 0
	113	10	Subcutaneously	26	23	19	33	88	73	127	1	110	29 0
Average		5	Intradermally					77	113	88			
		5	Subcutaneously					134	133	98			
		10	Intradermally					87	101	84			
		10	Subcutaneously					120	151	108			

It may be seen that the glycolytic activity does not run parallel to the blood sugar lowering effect. While the average blood sugar lowering effect of the intradermal injection at the first and second hour after the injection exceeds that of the subcutaneously administered insulin, the average glycolysis following intradermal injections is less at the first hour following the injection than before the administration of the insulin, and at the second hour is found only slightly increased above the first, initial value. The glycolysis following subcutaneous injection is increased at the first hour and still more so at the second hour following the injection.

This observation may indicate that the increase of the glycolytic activity is due to an increased concentration of the hormone in the circulation. The average decrease of the glycolytic activity after intradermal injection of insulin as compared to the glycolytic effect of a subcutaneous injection proves at least that there is no such increase, and points rather to a delayed adsorption of the insulin into the circulation.

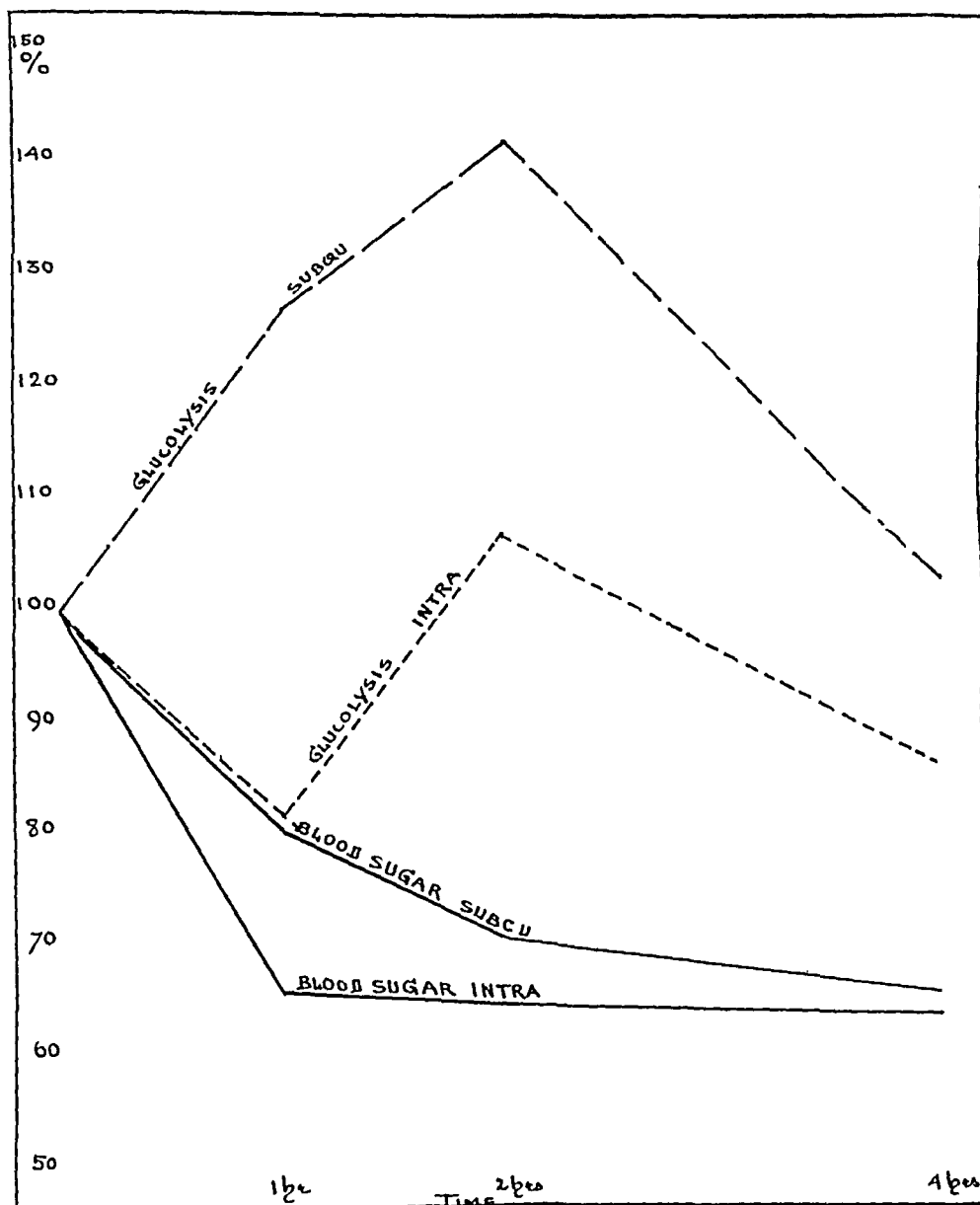


Chart 9—Composite curves of nine series showing effect of subcutaneous and intradermal insulin injections on the glycolytic activity of the blood (Table 4)

The observed average decrease of the glycolytic activity after the intradermal injection may be due to a defensive action or it may be due to a slightly lowered cell volume often observed to follow insulin injections. In view of the many factors that influence this activity a great many more experiments should be done before final conclu-

sions are drawn. The influence of dietary factors as well as the effect of hypoglycemia on glycolysis must be studied before any definite conclusions as to a relationship between the pancreatic hormone and the glycolytic activity of the blood *in vivo* can be reached. For instance, we have found the glycolytic activity of blood to increase from 30 to 50 per cent one hour after the intake of food as compared to the fasting condition. It has also been noticed that pronounced depression of the blood sugar level is followed by a material reduction in the glycolytic activity, probably due in part to the small concentration of the substrate. The negative results reported in the literature in the matter of increase in glycolysis following insulin injection may perhaps be explained from the foregoing. If the extent of glycolysis is determined at the height of insulin activity (e. g., during insulin shock) it will not be found increased but may be even depressed below the value found with a normal supply of substrate.

VIII

There would appear to be two possible ways by which insulin when in the circulation may exert its physiologic activity. 1. Fragmentation of the blood sugar molecule. 2. Contact with the liver, the muscles and perhaps other organs, which are stimulated to exert their normal activity in carbohydrate metabolism. When insulin is given intradermally, in which case, as has been shown in the twenty minute series, it has a decided effect on the blood sugar level before there can have been absorption of sufficient amount into the circulation, these two methods of action could not be held accountable for the observed effect.

The absorption of the effective hormone into the circulation is retarded when the insulin is administered intradermally. The demonstrated delayed absorption from the intradermal layers of the skin,⁵ as well as the results of the determinations of glycolysis of bloods taken after insulin injections, justify the assumption that the initial (twenty minutes) effect of the insulin given intradermally is due to an activity exerted before it has entered the circulation.

In the absence of insulin administration there are three known ways by which the blood sugar level may be decreased: (1) muscle activity, resulting in increased oxidation, (2) specific hyperfunction of the pancreas causing increased glucose catabolism, and (3) glycogen formation in the liver and in the muscles.

Muscle activity as a reason for the decrease in blood sugar observed in our tests can be eliminated. Tests on animals have shown that insulin, no matter how injected, is not effective if there has been muscular activity. Such an activity results in hyperglycemia which hides

for more than an hour any blood sugar lowering effect of the injected insulin⁶

The decrease of the blood sugar level at the first hour following intradermal insulin injection observed in diabetic cases can be explained by increased pancreatic activity only if large quantities of the pancreatic hormone were thereby caused to be introduced into the circulation. This again should lead to an increase in the glycolysis of the blood which did not manifest itself.

The third possibility mentioned is the lowering of the blood sugar level through increased glycogen formation in the liver and tissues. The first effect of an intradermal insulin injection may be such an increase in the glycogenetic function of the liver cells stimulated by a nerve pathway.

It is known that glycogen is formed rapidly. A 30 per cent loss in the blood sugar in one hour may be accounted for by glycogen formation. Such a decrease in an individual with a normal blood volume would mean that approximately 1.65 Gm of glucose had been polymerized into glycogen in this period.

Claude Bernard demonstrated that the liver receives autonomic impulses from the sugar center in the medulla which travel along the splanchnic nerve and cause the formation of glucose from glycogen with a resulting hyperglycemia. It is also known that parasympathetic stimuli lead to the formation of glycogen in the liver.⁷ If activation of the glycogenetic function of the liver cells occurs by way of a nerve action secondary to the injection of insulin into the skin, the chief or sole pathway of the stimulus must be by way of the parasympathetic fibers of the autonomic nervous system.

Eiger,⁷ working with turtles, showed that stimulation of the peripheral end of the cut vagus caused increased glycogenesis, despite exclusion of the pancreatic activity. Meyer⁸ showed that injection of pancreatic extract inhibits glycogenolysis in the liver. From these experiments it is to be assumed that stimuli may travel by way of the parasympathetic nerves to the liver and there cause actual increased liver cell metabolism, and also that such stimuli may travel to the pancreas, in this way an equivalent internal secretory influence of the liver cell metabolism may be registered. In both cases parasympathetic stimulation results in the inhibition of glycogenolysis.⁹ Minkowski's experiments have shown that not only extirpation of the pancreas but

6 Corbitt, H. B. *Am J Pharm A* **14** 108, 1925

7 Eiger, M. *Centralbl f Physiol* **30** 445, 1915

8 Meyer, H., in Mayer-Gottlieb. *Experimentelle Pharmakologie*, Berlin, 1922

9 Quoted from Muller, L. R. *Die Lebensnerven*, Berlin, Julius Springer, 1922

also disconnection of the nerves between the pancreas, the liver and the duodenum results in diabetic symptoms¹⁰

A brief period of hypoglycemia must follow glycogenesis. Clinical and experimental studies bear out the assumption that glycogenesis is responsible for an initial drop in the blood sugar level following intradermal insulin injection.

The glycogenetic function of the liver in health and in cases of mild diabetes is decreased if the liver is rich in glycogen, and the intradermal insulin effect has been found to be decreased in such cases after food intake. In severe diabetes the glycogenetic function of the liver is absent or much reduced and in such cases only a small difference, if any, between the two modes of administration could be demonstrated at the first hour period.

The difference in effect between the intradermal and the subcutaneous insulin injections in nondiabetic cases is small and variable, i. e., the subcutaneous injection may be more effective than the intradermal. This observation may also be explained on the basis of glycogen storage.

The smaller effect of the intradermal injections in severe diabetes as well as the absence of difference in effect between the two methods of administration in well nourished nondiabetic subjects can be explained by limitation of the glycogen forming potential of the liver cells.

Glycogen formation is limited in healthy subjects after eating because at that time glycogen is accumulated in the liver. In severe diabetes the function of glycogen formation is pathologically decreased. However, in either case decreased glycogenesis can only limit the blood sugar lowering process if this process consists, at least in part, in removal of the sugar from the circulation through glycogen formation. If it consists exclusively of fragmentation or oxidation of the glucose present in the blood and in the tissue fluids, the amount of glycogen present in the liver or the impairment of the glycogenetic function of the liver cells can have no influence.

Estimation of the respiratory quotient may be another method applicable to the determination of the question as to whether or not glycogenesis follows intradermal insulin injection. Glycogen formation from glucose does not increase the respiratory quotient whereas oxidation of glucose increases it. A difference in the insulin effect on the respiratory quotient shortly after the injection and at later intervals might be determinable by very exact experimental work. However, the brief period during which glycogen formation alone is responsible for the blood

10 Minkowski. Arch f exper Path u Pharmacol 30 371, 1893, *ibid* 53 331, 1905, Berl klin Wchnschr, 1890, No 8.

sugar lowering effect is so close to the injection itself that it would be difficult to obtain accurate results. Slight excitement of the patient, which is unavoidable after an injection, and the fact that within about thirty minutes the hormone action becomes effective would prevent a correct interpretation. Furthermore, the difference from the basal rate caused by the oxidation of about 1.5 Gm of sugar is too small to be measured by the clinical calorimetric methods at present at our disposal.

IX

The foregoing discussion leads to the assumption that a nerve stimulus resulting from an intradermal injection of insulin causes glycogenesis. Experimental evidence of the physiologic effectiveness of such a stimulus was obtained by blocking the particular nerve fibers.

The experiments were carried out with rabbits. The animals were injected with 10 mg of atropin per kilogram of body weight simultaneously with either intradermal, subcutaneous or intravenous insulin injections. The blood sugar of these animals as well as of control animals that did not receive the atropin injection, was determined half an hour after the injections. The effect of the intradermal injection on the blood sugar was much less in the atropinized rabbits than in the nonatropinized controls, the average showing 50 per cent difference. The average effect of the subcutaneous as well as the average effect of the intravenous injections of insulin was found to be the same in the atropinized as in the nonatropinized rabbits. The reason for this can only be that the nerve action of intradermally injected insulin is decreased or eliminated by atropin. In atropinized animals the hormone effect which follows absorption of the insulin into the circulation is the only mechanism of physiologic action, irrespective of the method of administration.

The results of these experiments are given in Chart 10.

The reduction in the hypoglycemic effect of an intradermal injection of insulin following the elimination of the nerve action by atropin is additional evidence that a nerve impulse is a prerequisite for the early insulin effect initiated by intradermal administration.

The use of epinephrin, which also blocks the parasympathetic nerves by increasing the tonus of the sympathetic, is of no value in such an experiment since one of its pharmacologic effects is increased glucose formation. The resulting hyperglycemia obscures the insulin effect. Pilocarpin in small doses increases the parasympathetic tonus, but is without influence on the insulin effect, and the usual difference between the intradermal and the subcutaneous insulin administration is observed when accompanied by injections of small doses of pilocarpin.

X

The quantitative determination of the urinary sugar excretion coincident with the blood sugar determinations following intradermal and subcutaneous insulin injections showed that the total amount of sugar excreted following an intradermal injection is decidedly less than that following a subcutaneous injection of a like dose under the same conditions. This lessened excretion cannot be solely attributed to the relatively greater and the quicker hypoglycemic effect of the intradermally injected insulin. The blood volume may be considered 88 per cent of the body weight. The total amount of blood sugar before insulin injection and at

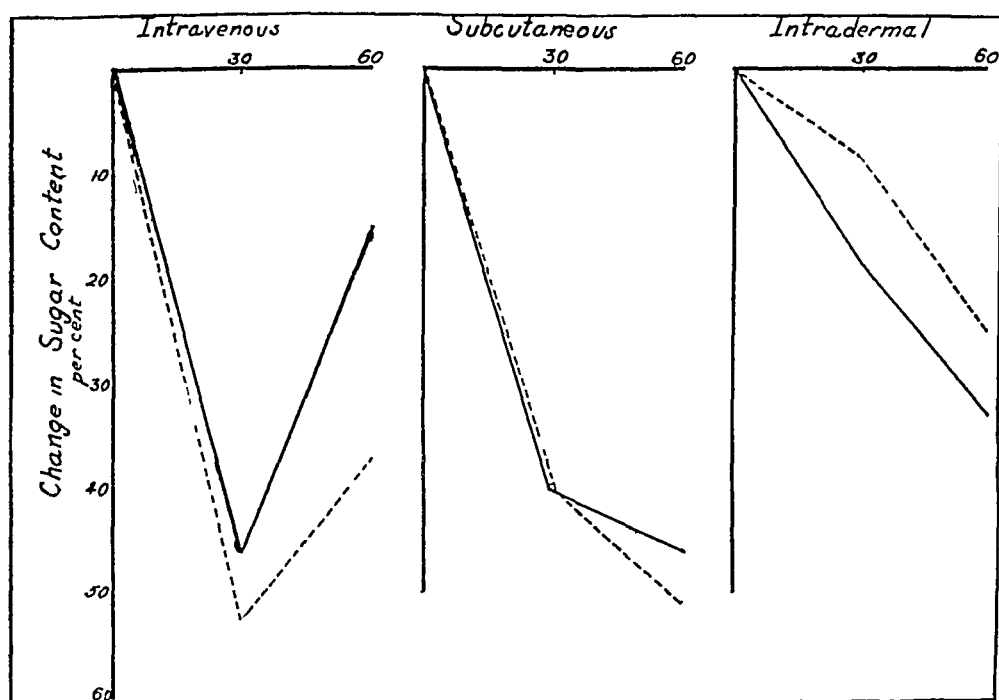


Chart 10—Average curves of a series of seven normal rabbits showing effect of atropin on action of insulin, solid line insulin injection alone, broken line atropin and insulin injection

stated intervals following the injection is obtainable from the blood sugar estimations. The difference in the amount of blood sugar lost and the amount of sugar excreted in the urine at a given interval following insulin injection represents the amount of sugar metabolized during this period less the indeterminable factor represented by the augmentation of the blood sugar by glycogenolysis or by resorption of sugar from the intestinal tract or body tissues. Adherence to standard conditions in these tests reduced this error to an almost constant quantity which, for the purpose of these experiments, may be ignored.

The average of the urinary sugar excretion and the coincident reduction in total in blood sugar in one and in four hours following intradermal and subcutaneous insulin injections are shown in Chart 11. While it must be remembered that the quantities determined can only be considered approximate, they demonstrate a distinct difference in the amount of sugar metabolized following the two methods of insulin injection. With a small dose, insufficient in its hormone supply, the difference between the two methods of injection is marked at the first hour and still definite at the fourth hour. With double the dose the difference is not quite as great at the first hour as with the smaller dose, but at the fourth hour, when presumably full absorption has taken place, the difference is materially decreased.

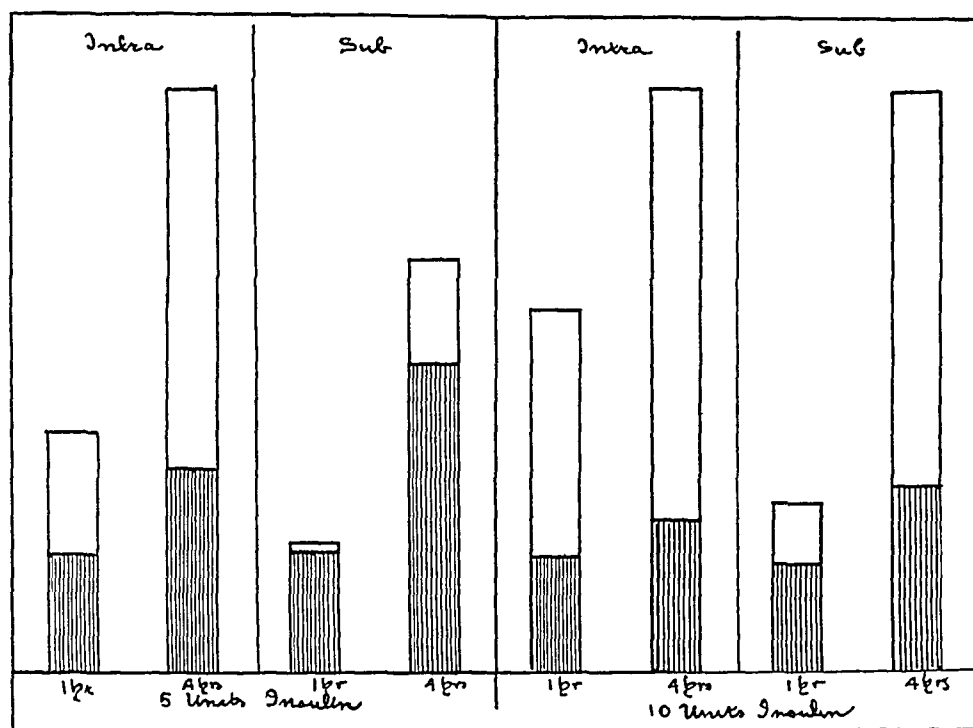


Chart 11—Diminution in total blood sugar following intradermal and subcutaneous insulin injections. height of columns represents reduction in total blood sugar, shaded portions represent urinary sugar excretion, unshaded portions represent sugar metabolized.

The striking differences following the two methods of injection again point to two different mechanisms of physiologic action which are especially apparent at the first hour after the insulin injection.

CONCLUSION

The results of the experiments reported in this article lead to the conclusion that insulin injected intradermally acts immediately by way of an autonomic nerve pathway on the liver, intensifying its glycoge-

netic function The effect of this stimulus is decreased or eliminated (a) if the glycogen storage in the liver is large, (b) if the glycogenetic function of the liver is pathologically decreased (severe diabetes), and (c) if substances are simultaneously injected which paralyze the parasympathetic fibers and thus disrupt this connection between the skin and the liver or if physiologically contrary stimuli overcome the parasympathetic impulses

The nerve stimulus continues to act on the liver as long as active insulin is present in the intradermal depot The glycogenetic activity of the liver at a given time does not depend on nerve impulses alone, the glycogen stores present in the liver as well as the severity of the diabetes are factors which must be considered when interpreting the differences obtained by the two methods of injection, in a given case

A hormone action of the insulin in the body fluids does not take place in the first interval following an intradermal injection The rate of absorption of insulin injected intradermally is slower than the rate of absorption of insulin injected subcutaneously and extends over a longer period As insulin is gradually absorbed from the intradermal depot into the circulation, the direct or hormone action is added to the nerve action Neither the point of onset of this hormone effect nor the period during which insulin is active exclusively by way of the nerve path are determinable from the blood sugar curves

In nondiabetic patients and in patients with mild diabetes glucose formation by glycogenolysis due to the depression of the blood sugar level caused by the injected insulin has to be considered when drawing conclusions from the results obtained at the first hour following the injection The hormone action of insulin in the circulation and in the tissue fluids is dependent only on the concentration, and the glucose formation by glycogenolysis secondary to depression of the glucose level below the normal must be taken into account

Stimulation of glycogenesis by a nerve pathway and the hormone effect on the glucose molecule are two distinct methods of insulin action The nerve effect is most prominent following the intradermal injection It may be present, but to a much less extent if insulin is injected subcutaneously Following an intravenous injection the nerve effect is almost entirely lacking This probably explains the relatively small therapeutic value of the intravenous route of administration Since the nerve effect, which stimulates glycogenesis in the liver, continues to act as long as active insulin is present in the skin, it is prolonged when absorption is delayed Gradual absorption will also result in a less intense but a more prolonged hormone action within the blood and tissue fluids Subcutaneous injections are not only followed by a less intense nerve effect but in addition, because of more rapid absorption, the hormone

effect is of shorter duration. Owing to the more rapid absorption the hormone effect is initiated at an earlier moment and sooner exhausted, especially if the dose is small. The amount of hormone entering the circulation after an intradermal injection of insulin depends on the extent of the loss of active material by adsorption.

The difference in effect found to result from different methods of insulin administration recalls the results of experiments in which non-specific agents were employed.¹¹ The injection of nonspecific, nontoxic albumin into the human body causes a reflex action on the involuntary nervous system. The closer the injection is made to the derma, the more pronounced is this reaction.

Insulin by way of the parasympathetic nervous system stimulates the glycogenetic function of the liver and possibly other cells possessing glycogenetic activity and thereby removes sugar from the blood stream. This nerve effect continues as long as active insulin is present in the depot. The possibility is suggested that such a glycogenetic impulse might originate from any body tissues containing active insulin and supplied with parasympathetic nerve connections.

It may be mentioned that a number of experiments have been reported which apparently show the relation of insulin to the involuntary nervous system, such as (a) action similar to choline on the mucous membrane of the intestines,¹² (b) disturbing actions on the electrocardiogram,¹³ and (c) blocking of insulin action by pharmacodynamic substances.¹⁴

Experiments are now being conducted to compare the known physiologic interrelation between the pancreas, the liver and other organs with the findings of the experiments which form the subject of this article. It has been shown that stimulation of the pancreas by nerve irritation leads to a stimulation of the glycogenetic function of the liver by way of nerve fibers recognized as parasympathetic or vasodilating. It is further known that under physiologic conditions the concentration of the pancreatic hormone in the circulation does not approach the concentration resulting from the injection of insulin in even moderate doses.

A sudden decrease of the blood sugar level in the circulation such as may be obtained by insulin injection creates impulses that act on the sugar center, and from here, in turn, impulses travel to the liver,

11 Muller, E. F. *Munchen med Wchnschr* **69** 1506 (Oct 27) 1922, *ibid* **69** 1753, 1922, *Involuntary Nervous System. An Important Factor in Body's Resistance*, *Arch Int Med* **35** 796 (June) 1925.

12 Dresel, K., and Zimmer, H. *Biochem Ztschr* **139** 463, 1923.

13 Von Haynal. *Klin Wchnschr* **4** 403 (Feb 26) 1925.

14 Magenta and Biosotti. *Compt rend Soc de biol* **89** 1125, 1923.

increasing the formation of glucose by local overbalance of the tonus of the sympathetic nerves ¹⁶

Insulin absorbed into the circulation lowers the blood sugar by increasing the glucose metabolism. The introduction of the pancreatic hormone into the circulation in large concentration cannot be compared to the normal physiology of blood sugar level regulation which depends on the equilibrium between glycogenesis and glycogenolysis. The nerve effect following an intradermal injection of insulin resembles the physiologic activity of the pancreas, while the increased direct hormone effect obtained after absorption cannot be considered the counterpart of the physiologic process.

The neural stimulation of glycogenetic activity cannot be separated from the hormone effect, but it is intensified by intradermal administration, while simultaneously the hormone effect, due to slower absorption and a certain increased loss by adsorption, is lessened. It remains to be seen whether better therapeutic results may be obtained by repeated intradermal administration of insulin, especially in the milder types of diabetes. It seems likely that a protracted intradermal treatment might be superior in therapeutic effect to the usual course of subcutaneous injections which do not stimulate the impaired function of the liver to the same extent. Such protracted glycogenetic impulses might lead to partial recovery or might at least check the progress of the disease. Severe cases in which there is great impairment or even absence of the glycogenetic function will remain the field for that method of insulin treatment which enhances glucose catabolism.

SUMMARY

A deposit of insulin in the body acts by a nerve stimulation which increases the glycogen forming function of the liver. This nerve stimulation is conducted parasympathetically. The effect is active as long as the insulin deposit exists as such. It is particularly strong if the insulin deposit is made in the skin because of its close relationship to the autonomic nervous system. The nerve effect is weaker after deposition of the insulin in organs in which absorption takes place rapidly, for instance, the subdermal tissues, and is lacking after intravenous administration. The hormone effect in the circulation and in the body tissues is relative to the dose but the neural effect of insulin does not depend on the dosage. Simultaneously with the beginning of the absorption from the insulin deposit and with the consequent entrance of insulin into the circulation the direct hormone effect is manifested. The nerve effect decreases simultaneously with the diminution of the insulin deposit outside of the circulation and disappears as the last part of the insulin deposit is absorbed.

¹⁶ Claude Bernard, quoted from Muller, L. R. *Die Lebensnerven*, Berlin, Julius Springer, 1924.

GASTRIC AND DUODENAL ULCER

THEORETICAL AND CLINICAL STUDIES¹

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Despite a tremendous amount of experimental, anatomic and clinical investigation, the problem of the pathogenesis of ulcer is not yet solved. A discussion of the various theories will not be attempted here. Only the general trend of thought will be indicated.

For many years ulcer was considered a local disease. It was thought that the original defect was produced by local causes such as vascular or traumatic lesions and that its chronic character was the result of the unrest and irritation inherent in the stomach. This theory still has many adherents, notably Aschoff.

A study of the recent literature, however, shows a tendency to consider ulcer a local consequence of a general bodily disturbance. For instance, von Bergmann¹ and his pupils, Westphal and Katsch,² following Eppinger and Hess, have found general "vagotonic" stigmas in ulcer patients. Friedman³ has added a "sympathicotonic" group. Peritz and Fleischer⁴ describe a "spasmophilia" of the whole person, while Kaufmann⁵ speaks of a "visceral tetany."

A consideration of the evidence of these authors makes it seem probable that these neuropathic and spasmophilic phenomena do play an important rôle in the pathogenesis of ulcer. It seems more probable, however, that the truth includes both views and that ulcer as a disease entity results from local plus general causes. The purpose of this article is not to propose a new theory but to analyze the problem more fully in an attempt to reconcile the various theories. It includes an outline of one method of attacking the problem and also the observations made thus far.

Ulcer of the stomach or duodenum may be defined as a loss in the continuity of the mucous membrane. Conceivably such a defect or erosion may be produced readily by various causes, traumatic, chemical, mechanical, thermal, bacterial, arteriosclerotic, embolic, thrombotic, toxic and hemorrhagic. It seems probable that ulceration at least superficial,

¹ From the medical department and the wards for the surgical treatment of diseases of stomach and intestines, Mount Sinai Hospital.

1 Von Bergmann, G. *Berl klin Wchnschr* **22** 524, 1918.

2 Katsch, G., and Westphal, C. *Mitt a d Grenzgeb d Med u Chir* **26** 391, 1913.

3 Friedman, G. A. *Peptic Ulcer*, *J A M A* **71** 1543 (Nov 9) 1918.

4 Peritz, G., and Fleischer, F. *Arch f Verdauungskr* **32** 243, 1923.

5 Kaufmann, J. *Am J M Sc* **165** 67 (July) 1923.

is brought about by one or the other of these agents in almost every human stomach. These ulcers, in most cases, apparently heal completely, promptly, and without visible scarring. In some persons, however, such a primary erosion fails to heal and assumes the pathologic characteristics of round ulcer of the stomach or duodenum. It may remain superficial or progress deeper, may almost heal and then break down, or it may heal and recur. Whatever its outcome, however, it is chronic and this is its chief characteristic. In the experimental animal one may cause or institute an erosion or ulcer, but it invariably heals. If a piece of mucous membrane is excised with its submucosa and muscularis, leaving only the serosa intact, such an experimental ulcer in the dog's stomach invariably heals perfectly within a few weeks. Briefly, the most important feature of ulcer is not the cause of the primary erosion but its failure to heal. The solution of the ulcer problem will probably be found in a study of the conditions that tend to retard or prevent the process of healing. It is one of the purposes of this article to emphasize this phase of the problem.

Many theories have been advanced to account for the chronicity. These include (1) irritation (ingesta, acid, peristalsis), (2) infection (bacteria, toxins, fungi), (3) devitalization (thrombosis, embolism, arteriosclerosis, hemorrhage, angiospasm, myospasm), with subsequent digestion by acid and pepsin or regurgitated trypsin, (4) absence of substances (antipeptic ferments, mucus) that normally protect the gastric mucosa from autodigestion, (5) congenital weakness of the tissues locally (intestinal or other cell rests, malformations, arrested development), (6) mechanical irritation (at the "magenstrasse" and the isthmus), and (7) disturbances of the vegetative nervous system (vasomotor instability, hyperperistalsis, hypersecretion, myospasm). These are the most important theories. As yet, however, an explanation of the cause of chronic ulcer which harmonizes with the clinical and pathologic facts does not seem to be at hand.

A rational approach to the problem would seem to be a study of the physiology of inflammation with reference to the factors that may retard healing processes. What conditions—local or general—exist in these patients which may interfere with the normal or physiologic repair phase of the inflammatory process? This question involves difficult and unsettled problems concerning the physiology of inflammation. There are, nevertheless, certain valuable observations that concern our problem.

Undoubtedly, constant irritation of an injured site delays or prevents healing. Also a decreased vascular supply acts similarly. Conversely, lack of irritation and a good circulation locally seem to hasten the process of repair. There seems to be considerable evidence, furthermore, that the repair phase, at least, is largely dependent on vasomotor and other visceral nerve influences.

The general tendency of the investigators of repair in peptic ulcer has been to study the factors that irritate the sensory or afferent nerves. It has been repeatedly suggested that the mechanical, chemical and thermal irritation of food, the presence of acid and pepsin, and the tonic and peristaltic changes in stomach and duodenum supply the numerous sensory impulses that prevent the healing of the ulcer. This explanation, however, does not seem sufficient when we recall that these factors may be constantly present and yet a large number of more or less superficial ulcers or erosions presumably occur in the human stomach and apparently heal promptly and perfectly. Also the constant healing of such ulcers experimentally produced in animals would tend to substantiate this theoretical observation.

It seems more probable that a consideration of the motor responses to these sensory stimuli may lead us further in the problem. There is evidence, clinically, that there may exist locally a disturbance in the motor response in the direction of excess. For, in most cases, hyperperistalsis, hypersecretion, hypertonus, localized myospasm, and pylorospasm are present at some time or throughout the disease. Furthermore, arteriolar and capillary constriction, and spasm of the muscularis mucosa probably exist without being evident clinically. A consideration of the physiology of inflammation makes it probable that this local state of excessive motor response or overirritability interferes with healing. Theoretically this local overirritability might result from local or general causes: (1) repeated and excessive sensory stimuli, (2) overirritability of the responding tissues, (3) increased irritability at the synapses (peripherally or in the spinal cord), (4) intensification of the motor outflow by the higher centers (medullary or cerebral), (5) increased sensitiveness or response of the myoneural junctions or nerve ends.

Conceivably, a combination of the presence of an ulcer and a general bodily overirritability of nerves and tissues would produce all these causes. Actually, our clinical studies (outlined below) make it seem probable that the local manifestations not only result from the ulcer but are part of a general preexisting overirritability.

Since we have already assumed that the primary erosion may be produced readily by a variety of agents, the possible causes of general overirritability will be next considered. One may mention the following: (1) alkalosis (diet, administration of alkalis, hyperpnea, loss of gastric secretion, constitution), (2) parathyroid disturbance (parathyroidectomy, functional or organic disease of the parathyroids leading to insufficiency, ductless gland imbalance), (3) toxic agents (from intestinal putrefaction, guanidine salts, ergotoxin, cocaine, caffeine, unknown toxins), (4) disturbance in the calcium metabolism (decreased ionizable calcium in the blood and tissues brought about in various

ways), (5) vegetative nervous system (excessive lability, "imbalance," overirritability of centers, nerves, myoneural junctions or nerve ends, relation to the ductless glands, relation to the hydrogen and other ion balances), and (6) psychic influences (involving the voluntary and involuntary nervous system and ductless glands) These seem to be the most important conditions disposing to an overirritability either in the nervous system or the tissues themselves It is our intention to investigate in the future these possibilities, both clinically and experimentally At the present it seems to us more probable that a condition of mild or latent tetany, or a similar condition, or a disturbance of the vegetative nervous system, or a combination of these, may be the general bodily characteristic that interferes with the healing of ulcer

The following studies, therefore, were made on patients (1) the response to electrical stimulation (galvanic), (2) the mechanical irritability of muscle and nerve (the "idiomuscular contraction" and Chvostek sign), (3) the amount of total calcium in the blood, (4) the symptoms and signs of disturbance in the vegetative nervous system, and (5) the pharmacologic stimuli of the vegetative nervous system (using epinephrine and atropine) It is proposed eventually to carry out, in addition, the studies given in table 1

TABLE 1—*Future Studies*

Capillaroscopy	Sensory thresholds to pain and touch
Reflexes	State of hair, teeth, nails
Habitus	Hydrogen, calcium, phosphorus and chloride concentration in blood
Nonprotein nitrogen bodies in the blood	Alveolar and blood carbon dioxide tension
Familial tendencies	Alkaline tide in urine and blood
Pilocarpine reaction	

The patients selected for the present study were those with ulcer of the stomach or duodenum proved clinically, roentgenographically, and in most cases surgically Normal subjects and a few symptomless postoperative ulcer cases were included A number of patients with gastric symptoms, with negative roentgen-ray and surgical findings ("gastric neurosis"), also were observed The entire group were male adults

ELECTRICAL IRRITABILITY

Method—A 1 cm electrode of the usual galvanic battery was applied to the ulnar nerve between the olecranon and the internal condyle The cathodal closing current was gradually increased until a perceptible contraction of any innervated muscle was noted The anodal closing contraction was similarly obtained Opening contractions under 5 milliamperes were not obtained and currents over this, being too disagreeable to the patients, were not applied The same apparatus (Wappler) and technic were used throughout

Studies—1 Normal controls (male adults) were used and forty patients tested. A current over 3 milliamperes for a cathodal closing contraction was required by 82 per cent.

2 Ulcer patients were used, and sixteen patients tested. Of these 87 per cent reacted to a cathodal closing current under 3 milliamperes.

3 Gastric neurosis was studied, and seven patients tested. Five reacted under 3 milliamperes.

MECHANICAL IRRITABILITY

Method—The facial nerve was tapped at the ear, over the parotid, and at the zygomatic arch, and the facial, eye and mouth muscles observed for the twitching response (Chvostek's sign). The biceps muscle belly was struck smartly with the finger tip or a small percussion hammer, and the appearance of a lump (so-called idiomuscular contraction) or fibrillary twitchings noted. A positive Chvostek sign with marked lumping or twitching was designated as a strongly positive reaction.

TABLE 2—*Calcium in the Blood*

		Mg per 100 Cc			Mg per 100 Cc
1	Pyloric stenosis, ulcer	10.0	9	Duodenal ulcer	11.4
2	Duodenal ulcer	10.0	10	Duodenal ulcer	10.2
3	Duodenal ulcer	10.5	11	Duodenal ulcer	9.0
4	Duodenal ulcer	10.9	12	Duodenal ulcer	10.3
5	Duodenal ulcer	10.0	13	Duodenal ulcer	10.3
6	Duodenal ulcer	10.9	14	Duodenal ulcer	10.7
7	Duodenal ulcer	10.8	15	Duodenal ulcer	10.0
8	Duodenal ulcer	9.3	16	Duodenal ulcer	11.1

Studies—Normal controls were used, and eighty patients tested. Sixty-eight, or 85 per cent, were negative. The twelve positive cases were markedly emaciated, miscellaneous postoperative cases.

Twenty-six duodenal ulcer patients were tested. Seventeen, or 65 per cent, reacted strongly, eight, or 30 per cent, moderately, and one was negative.

Eleven gastric ulcer patients were tested. Six reacted strongly and five moderately.

Gastric neurosis was studied, fifteen patients being tested. Ten, or 66 + per cent, were negative, four slightly and one strongly, positive.

TOTAL CALCIUM IN THE BLOOD

Method—Dr Lewis T. Mann carried out the Kramer-Tisdall method for determining total calcium in the blood serum of sixteen patients (table 2). The normal concentration of calcium in the blood is from 10 to 11 mg per hundred cubic centimeters.

DISTURBANCE OF THE VEGETATIVE NERVOUS SYSTEM

Method—All the symptoms and signs that are associated with abnormal functioning of the vegetative nervous system were systematically looked for (table 3). Cases with several of these signs and symptoms, which were quite obviously instances of a disturbed involuntary nervous system, were considered strongly positive. Because it is as yet undecided whether the gastro-intestinal symptoms are primary or secondary in ulcer, they were disregarded.

Studies—Duodenal ulcer was studied, twenty-five patients were tested. Twenty-two, or 88 per cent, were negative, two slightly positive, and one strongly positive.

Eleven gastric ulcer patients were studied. Ten were negative, one slightly positive.

Gastric neurosis was studied, nineteen patients being tested. Seventeen, or 89 per cent, were strongly positive, and two were negative.

TABLE 3—*Vegetative Nervous System Signs and Symptoms*

Miosis, Mydriasis	Aschner reaction
Epiphora, Dryness	Tschermak reaction
Exophthalmos,* Enophthalmos	Atropine reaction*
Narrow fissure, Wide fissure	Epinephrine reaction*
Pallor,* Flushing*	Unrest
Dermographism,* Pigmentation*	Asthma
Salivation,* Dryness*	Cardiospasm, dysphagia
Size of thyroid and tonsils	Mucus colitis, biliary colic
Blood pressure, low* or high	Drug and food idiosyncrasy
Bradycardia,* Tachycardia	Seasonal variation of symptoms*
Respiratory arrhythmia Palpitation	Libido
Narrow arteries, eosinophilia	Asthenia*
Dry, or cold*, clammy hands	Headache
Hypermotility,* Atony	Dizziness
Constipation,* Diarrhea	Hyperhidrosis*
Loewi reaction	

* Symptoms most frequently encountered

PHARMACOLOGIC STIMULATION OF THE VEGETATIVE
NERVOUS SYSTEM

Method—1 Epinephrine 0.5 cc of a fresh, 1:1,000 epinephrine (adrenalin, Parke, Davis & Co) was given subcutaneously. Blood pressure readings were taken before the injection until a level was maintained and after the injection every minute until the original level was restored. A rise in the systolic pressure of 20 mm or more, or a small rise (from 10 to 20 mm) if accompanied by severe general symptoms, was considered a strongly positive reaction.

2 Atropine Atropine sulphate (1 mg) was administered subcutaneously and the pulse rate, pupils and symptoms observed for one hour. A rise in the pulse rate of 20 or more with dilated pupils and dryness was considered a strongly positive reaction.

Studies—(a) Normals Peabody and others⁶ in a study of epinephrine sensitiveness found that 14 per cent of normals gave a positive reaction Kessel and Hyman,⁷ while studying these drug reactions in exophthalmic goiter, found that 30 per cent of normal persons react to epinephrine and 22 per cent to atropine

(b) A summary of the patients tested is given in table 4

COMMENT

Compared to normal persons, patients with gastric or duodenal ulcer tend to respond excessively to various stimuli A survey of the foregoing studies indicates that from 60 to 80 per cent of the ulcer patients

TABLE 4—*Summary of Patients Tested*

Disease	Patients	Drug	Reaction			
			Strong	Moderate	Weak	Negative
Duodenal ulcer	15	Epinephrine	5	4	5	1
Duodenal ulcer	11	Atropine	9	2	—	—
Gastric ulcer	8	Epinephrine	5	1	2	—
Gastric ulcer	7	Atropine	6	1	—	—
Cured ulcer	8	Epinephrine	6	1	1	—
Cured ulcer	8	Atropine	8	—	—	—
Gastric neurosis	10	Epinephrine	7	1	1	—
Gastric neurosis	6	Atropine	4	2	—	—

react to small galvanic currents, possess marked nerve and muscle irritability, and give an exaggerated response to epinephrine and atropine

This study shows, in addition, an almost complete absence of the signs and symptoms of a disturbance of the vegetative nervous system in these patients Vagotonia and sympathicotonia, or "autonomic imbalance,"⁷ as definite clinical states, were not encountered An occasional symptom or sign was found which did not seem enough to distinguish these patients from normal persons In marked contrast to the ulcer patients, the cases of "gastric neurosis" are practically all outspoken examples of a disturbed vegetative nervous system They present many or most of the stigmas (table 3) Also they react excessively to electrical and pharmacologic stimulation but only rarely to mechanical stimulation The relationship of these two groups is not clear The neuroses do not seem to merge with the ulcer group We believe that this distinction may prove of great value clinically in differentiating ulcer from neurosis In fact, it has been possible recently to predict correctly the operative findings in a few doubtful cases This clinical application is now being actively investigated

6 Peabody, F W, Sturgis, C C, Tompkins, E M, and Wearn, J T Am J M Sc **161** 508 (April) 1921

7 Kessel, L, and Hyman, H T Am J M Sc **165** 513 (April) 1923

It may be suggested that the general overirritability is the result of the lesion and not the underlying cause of the chronicity. To decide this it will be necessary to observe patients with ulcer symptoms, and later the same patients when cured, preferably surgically. To date we have studied only four such cases, they presented, while well, the same signs of overirritation. We have also studied eight cases in which ulcers were removed surgically. The symptoms were relieved, but the overirritable condition was nevertheless still present. It would be of interest in this connection to see whether the few ulcer patients with little or no overirritability heal or lose their symptoms more promptly.

We do not know as yet the explanation of the overirritability. It seems to be closely related to both tetany and the vegetative nervous system. With reference to tetany, it may be said that this condition in its various forms presents a perplexing problem. It appears that the parathyroids, certain toxins and the ion balance in the blood and tissues probably are all involved. We found normal total calcium figures in the blood, but tetany may occur with normal calcium figures. It is agreed that the disturbance is in the ionizable calcium and we have no method of estimating this at present. The involvement of the vegetative nervous system in tetany as well as its functional disturbances in general also are complex problems. Although it is well known that the parasympathetic and sympathetic may be imbalanced, or both may respond excessively to stimuli, the explanation of such states is as yet unknown.

In general, it is our impression that a mild or a latent tetany, or a closely related state, with a secondary involvement of the vegetative nervous system, is the underlying cause of the failure to heal in ulcer of the stomach or duodenum. Whether it depends ultimately on a parathyroid disturbance cannot be answered in the present state of our knowledge. Experimental work on animals is now being carried on in the surgical laboratories of the Columbia University College of Physicians and Surgeons in which the effect of such general disturbances as mentioned here on the rate of healing of artificially induced gastric mucosal defects is being studied.

SUMMARY

- 1 Superficial ulcers or erosions of the stomach or duodenum occur owing to various local and general causes, but heal perfectly in most persons.

- 2 In certain subjects the lesion progresses and takes on the features of chronicity. This is the characteristic of ulcer as a disease entity.

- 3 The usual explanations, mostly referable to local conditions, for the failure to heal seem incomplete. It is suggested that some general bodily condition, interfering with the physiology of healing, may be present.

4 An excessive response to stimuli on the part of the nerves and tissues, locally or generally, may furnish such interference to healing. Tetany or a related condition, a disturbance of the vegetative nervous system, or a combination of both, are possible causes of the supposed general overirritability.

5 Patients with ulcer, with gastric neurosis, and controls were tested with various stimuli to ascertain the presence of such overirritable states.

6 Almost all the ulcer patients respond excessively to mechanical, electrical and pharmacologic stimulation. Patients with gastric neurosis react similarly, except to mechanical stimuli, but present a marked contrast to the ulcer group in that they display obvious stigmas of a disturbed vegetative nervous system. This distinction may prove useful clinically.

7 The persistence of the overirritability after a surgical cure suggests that it is a general bodily state, probably constitutional, and not merely the result of the presence of the ulcer.

THE THERAPEUTIC USE OF DIETS LOW IN WATER AND IN MINERAL CONTENT^{*}

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The importance of a diet low in chlorides for certain cases of nephritic edema was demonstrated by Widal¹ in 1903. In his cases chlorides were readily retained, but equal retention of water was not shown. The ingestion of a diet low in chlorides was followed by diuresis and loss of edema. In our experience, in cases of obstinate edema due to renal disease inability to excrete both chlorides and water usually was manifested and thus the so-called salt-free diet failed to produce diuresis and loss of edema. While considering possible dietetic reasons for this failure, we found by analysis that our routine salt-free diet contained a small quantity of chloride, from 2 to 3 Gm, but from 1,200 to 1,400 cc of water. This amount of water when added to that ingested as fluid, from 600 to 1,000 cc, made the daily intake from 1,800 to 2,400 cc. In revising the diet we hoped (1) to decrease the water contained, (2) to reduce the amount of sodium, since sodium retention has been shown to be associated with water retention, and (3) so to control the diet that this minimal content of water and mineral would be, for practical purposes, the same from day to day. Such a diet has been used in the wards of St Mary's Hospital for the last two years and has proved a most effective adjunct in the treatment not only of cases of obstinate edema due to nephritis but also of those of persistent ascites due to hepatic and cardiac disease. The object of this paper is to show that the administration of such a diet is a useful therapeutic measure, that important quantitative data can be thus obtained and that after its continuation for several months there is no apparent evidence of diet deficiency.

COMPOSITION OF THE DIETS

Type of Food—When a patient with nephritis enters the hospital he is placed on a diet calculated to meet the basal requirements of the average adult. Such a diet contains 40 Gm of protein and 1,500 calories. Basal diets for patients with nephritis in the department of medicine at St Mary's Hospital are planned on a foundation diet con-

^{*} From the division of medicine, Mayo Clinic.

¹ Widal, F, and Javal, A. La cure de dechlorination, son action sur l'oedeme, sur l'hydratation et sur l'albuminurie a certaines periodes de la nephrite epitheliale. Bull et mem Soc med d hôp de Paris 20 733-749, 1903.

taining 800 Gm of fruits and vegetables, 100 Gm of bread and 20 Gm of dry cereal. This basis contains approximately 20 Gm of protein. To this is added food containing complete proteins to make up the required 40 Gm, and carbohydrates and fats to produce 1,500 calories. These diets contain between 1,200 and 1,400 Gm of water as calculated from the percentage composition of water in the foods served. Diet 1, table 1, shows the mineral content of the basal diet for patients with nephritis. This is our routine salt-free diet. To make it more palatable for patients who have nephritis without edema, 5 Gm of extra salt was added during the process of preparation.

Because these diets contained considerably more water than we had anticipated, they were first modified by lowering the water content of the food. Eight hundred grams of water was the standard accepted. Foods with a low water content were selected and a diet formulated which contained 40 Gm of protein, 1,500 calories. Later the mineral content of the food was calculated. It was found to be rather uniformly low in all mineral salts except those of potassium. This was high, as

TABLE 1—*Composition of the Diet*

Diet	Carbohy- drate, Gm	Pro- tein, Gm	Fat, Gm	Calo- ries	Water, Cc	So- dium, Gm	Potas- sium, Gm	Cal- cium, Gm	Magne- sium, Gm	Chlor- ine, Gm	Phos- phorus, Gm	Sul- phur, Gm	Iron, Gm
1	189	37	65	1,531	1,286	1 156	3 745	0 807	0 312	1 585	0 991	0 736	0 013
2	148	40	80	1,515	809	0 507	1 625	0 225	0 196	0 668	0 657	0 562	0 009
3	243	40	92	2,016	834	0 528	1 637	0 328	0 212	0 693	0 666	0 569	0 009
4	175	50	126	2,094	872	0 747	1 772	0 292	0 208	0 867	0 741	0 692	0 011
5	235	50	144	2,508	895	0 770	1 872	0 307	0 223	0 888	0 751	0 700	0 011

potato had been used in generous amounts because of its high carbohydrate content. Rice or macaroni was then substituted for the potato in the diet, and the potassium content was reduced considerably (diet 2, table 1). This diet contains 600 Gm of fruits and vegetables. No evidence of deficiency of mineral or vitamin has appeared in patients who have been on this diet for several months. In selecting foods to fill the diet prescription we made an attempt to secure foods that would be available for a long period of time in order that the diet might be held constant. Fresh fruits and vegetables were used whenever possible. At least 400 Gm of the amount allowed was served as fresh fruit and green vegetables. Orange, grapefruit, banana, lettuce, tomato and string beans were used. Canned tomatoes and canned string beans also were used, standard brands having been selected for analysis. All food was prepared and served without extra salt. The foods served were weighed and the uneaten portions were reweighed. A permanent record of the diet actually eaten was calculated and charted. The actual fluid ingested over and above that in the food was from 600 to 800 cc daily, making the total fluid intake from 1,400 to 1,600 cc.

After the caloric requirement and the ability of the patient to use protein food had been determined, the diet was adjusted to meet the actual requirements of the individual. This necessitated the calculation of several standard diets. An attempt was made to hold the water and mineral content as nearly constant as possible while the protein and calories were increased (diets 3, 4 and 5, table 1). Two thousand calories, diet 3, was suitable for a group of patients who were able to be up and required about 30 per cent more than their basal calories, without an increase in protein allowance, the increased fat and carbohydrate acting as spacers of body protein. Diet 4 (table 1) was calculated for the patient needing 50 Gm of protein daily. Diet 5 (table 1) shows the increase in water and minerals necessary to allow the patient 50 Gm of

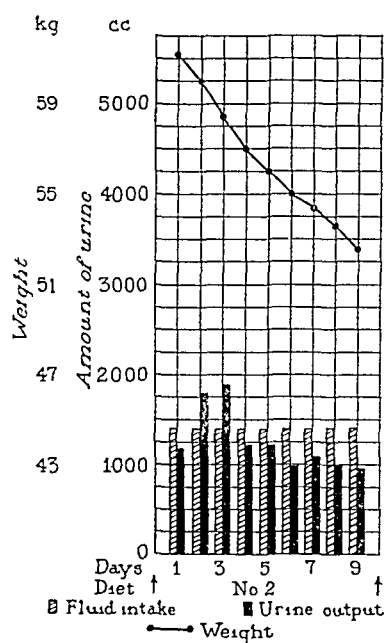


Chart 1 (case 1) — Findings in chronic nephrosis

protein and 2,500 calories daily. As the protein and calories in the diets increased over the basal, a slight increase in water and mineral content occurred. Calories were increased by adding sugar and fat. Egg and milk protein were used to increase the protein content of diets 4 and 5.

A number of menus for varying the methods of preparing and serving the diets were planned. Patients were taught how to prepare these diets at home, and each was provided with a pair of gram food scales and instructed in their use. Quantitative diet sheets were written for these patients and lists of substitutions provided for everyday use. Food values and diet calculation were taught to the patient or to some member of his family but, with a diet holding thirteen factors constant, the variety of food is necessarily limited. These patients have been

successful in following instructions at home and have become adjusted to the dietary limitations. Table 2 gives the quantities of the individual articles of food for a single day.

Chemical Content—Analysis of the water and mineral content of the particular foods served in the weighed low salt, low fluid diet (diet 2) was undertaken because of the significance the minerals are believed to have in the dietary treatment of the cases described, also to determine whether analysis with the newer micro methods would yield data that would corroborate the results obtained by previous workers, especially those used by Sherman² in his tables. It was believed that should the methods used by us for mineral analysis give results reasonably close to the accepted standards for the mineral content of foods such as Sherman has compiled, we would be justified in using them for purposes of calculation.

In table 3, Sherman's figures and our data are compared. In most cases the two are remarkably close, but nearly every food shows varia-

TABLE 2—*Weighed Low Salt, Low Fluid Diet (Diet 2, Table 1)*

Breakfast	Gm	Dinner	Gm	Supper	Gm
Ten per cent fruit	100	Five per cent vegetable	100	Five per cent vegetable	100
Eggs (one)		Rice	100	Macaroni	100
Toast	20	Banana	100	Fifteen per cent fruit	100
Butter	10	Meat	45	Ten per cent fruit	100
Sugar	5	Mayonnaise	15	Bread	20
		Bread	20	Butter	15
		Butter	15	Eggs (one)	
		Sugar	5	Mayonnaise	15
				Sugar	5

tion, sometimes to a considerable extent in one or more of the minerals. The greatest differences occurred in the case of dried fruits. Discrepancies in these foods were not unexpected because the manner of drying and the degree to which they are dried offer considerable chances of error. Hence, whenever possible these foods are not included in diets served during periods when accurate studies are being made.

For studies such as those reported here, in which no special attempt has been made to determine with great accuracy the mineral balance, the use of standard figures for purposes of calculating the approximate daily intake of mineral and water seems justifiable.

Determinations of the inorganic acid and basic ions, urea nitrogen, ammonia nitrogen and total nitrogen of the urine were made in two normal persons and two patients with edema and ascites who were receiving diets 2 or 4. Daily estimations were made during the four experiments and listed for the two patients, but only the values of the first

2 Sherman, H. C., and Gettler, A. O. The Balance of Acid-Forming and Base-Forming Elements in Foods, and Its Relation to Ammonia Metabolism, *J Biol Chem* **11** 323-338, 1912.

and last day of the two normal controls are given. The daily inorganic and nitrogen content of the diet also is given (table 4). This table shows the decrease in the excretion of the inorganic salts and ions which occurs when a normal person changes from an ordinary mixed diet to one low in mineral content. On the fifth day of experiment with subject 6 and on the third day of experiment with subject 5 the total nitrogen of the urine approximates that in the diet. Similar nitrogen values were obtained in case 1. In the normal controls the output of chlorine and sodium reached values close to those of the dietary intake on the third and fifth days, respectively.

The results obtained in cases 7 and 1 are included to show by contrast how the daily urine excretion of chlorine and sodium in abnormal cases continued to be persistently higher than the intake. This excess excretion of chlorine and sodium is due in part to the abnormal storage

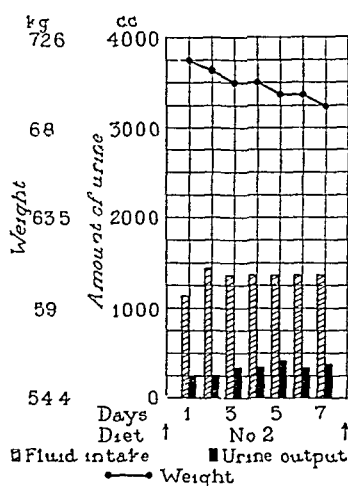


Chart 2 (case 2) — Findings in Banti's disease with ascites

of these ions in the tissues of these patients. Such a continued net loss of chlorine and sodium also emphasizes the therapeutic value of the diet.

USE OF THE DIETS

Up to the present we have used the low salt, low fluid diet in eight cases of subacute or chronic nephritis with marked edema and twenty-five cases of chronic ascites with liver diseases or with liver disease and cardiac insufficiency. In many of these cases satisfactory diuresis was produced by the combined use of the diet, ammonium chloride and novasurol³. In a case of chronic nephrosis (case 1, table 4, chart 1) spon-

3 Keith, N. M., Barrier, C. W., and Whelan, Mary. The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, *J. A. M. A.* 85: 799-806 (Sept. 12) 1925. Rowntree, L. G., Keith, N. M., and Barrier, C. W. Novasurol in the Treatment of Ascites in Hepatic Disease, *J. A. M. A.* 85: 1187-1193 (Oct. 17) 1925.

TABLE 3—Food Analysis

Food	Water, Grams per Cent		Sodium, Grams per Cent		Potassium, Grams per Cent		Calcium, Grams per Cent		Magnesium, Grams per Cent		Chlorine, Grams per Cent	
	Atwater and Bryant ⁴		Clinic	Sherman	Clinic	Sherman	Clinic	Sherman	Clinic	Sherman	Clinic	Sherman
	Clinic	Bryant ⁴										
Orange	86.8	86.9	0.0138	0.012	0.156	0.177	0.021	0.015	0.008	0.012	0.008	0.006
Orange juice	85.9		0.009	0.003	0.200	0.182	0.015	0.029	0.014	0.011	0.014	0.003
Grapefruit	90.8		0.006	0.004	0.164	0.161	0.010	0.021	0.007	0.009	0.009	0.005
Banana	72.0	75.3	0.030	0.034	0.408	0.401	0.006	0.009	0.028	0.028	0.126	0.125
Apple	85.9	84.6	0.015	0.011	0.123	0.127	0.011	0.007	0.006	0.008	0.037	0.005
Beans	94.3	93.7	0.015	0.019	0.160	0.247	0.052	0.046	0.019	0.025	0.024	0.024
Lettuce	96.2	94.7	0.0272	0.027	0.209	0.339	0.028	0.043	0.011	0.017	0.056	0.074
Tomato	92.0	94.3	0.024	0.010	0.280	0.275	0.006	0.011	0.011	0.010	0.058	0.034
Potato	74.3	75.5	0.018	0.021	0.501	0.429	0.021	0.014	0.019	0.028	0.027	0.038
Rice	70.6	72.5	0.012	0.025	0.046	0.070	0.020	0.009	0.033	0.033	0.056	0.054
Macaroni	76.6	78.4	0.0095	0.008	0.054	0.130	0.036	0.022	0.038	0.037	0.077	0.073
Bread, salted	29.7	35.6	0.517	0.394	0.110	0.108	0.040	0.027	0.028	0.023	1.09	0.607
Bread, salt free	10.3	35.6	0.067	0.394	0.070	0.108	0.016	0.027	0.013	0.023	0.116	0.607
Bread, whole wheat, salt free		38.4	0.034		0.108	0.011	0.011		0.039		0.031	
Steak, porterhouse	47.0	52.4	0.409	0.067	0.402	0.271	0.066	0.009	0.025	0.018	0.045	0.060
Egg white	84.7	86.2	0.190	0.156	0.137	0.160	0.012	0.015	0.012	0.010	0.163	0.155
Egg yolk	50.1	49.5	0.114	0.075	0.109	0.115	0.125	0.137	0.014	0.016	0.050	0.166
Butter, salted	35.0		0.929	0.788	0.019	0.014	0.016	0.015	0.002	0.001	0.935	1.212
Butter, salt free			0.069		0.004	0.014	0.003	0.015	0.050	0.001	0.162	
Salad dressing	7.6		0.041		0.008	0.009	0.008		0.002		0.056	
Sugar	0.0		0.001		0.004	0.004	0.008		0.003		0.033	
Fig	14.0	18.8	0.081	0.046	0.647	0.994	0.143	0.162	0.054	0.071	0.198	0.043
			0.072		0.742		0.180		0.058			
Raisin	22.0	14.6	0.076	0.133	0.694	0.820	0.161	0.064	0.056	0.083	0.066	0.082
			0.099		0.648		0.023		0.025			
			0.103		0.909		0.063		0.044			
Date	16.7	15.4	0.101	0.055	0.799	0.034	0.043	0.047	0.034	0.069	0.268	0.228
			0.049		0.611		0.065		0.069			
			0.048		0.490		0.037		0.046			
			0.049		0.500		0.035		0.046			

TABLE 4—Comparison of Intake in Food and Output in Urine

Case	Age	Sex	Diet	Date, Urine, Ce	Chlorine, Gm		Sulphur, Calculated as SO ₃ , Gm		Phosphorus, Gm		Sodium, Gm		Potassium, Gm		Calcium, Gm		Magnesium, Gm		Ammonium Nitro gen, Gm		Total Nitrogen, Gm		Diag nosis	
					In take	Out- put	In take	Out put	In take	Out put	In take	Out- put	In take	Out put	In take	Out put	In take	Out put	In take	Out put	In take	Out put		
5	29	M	1	6/23	500	0 87	2 33	1 698	1 22	0 741	0 465	0 747	1 61	1 772	1 25	0 292	0 16	0 208	0 085	0 365	6 1	8 0	7 6	Con trol
				6/25	450	0 86	0 86	1 105	1 15	0 662	0 662	0 35	0 35	1 83	1 33	0 18	0 18	0 120	0 393	6 1	8 6	8 6		
6	29	M	2	4/28	975	0 67	3 68	1 405	0 66	0 76	0 51	2 22	1 62	2 28	0 23	0 144	0 20	0 092	0 36	8 09	6 4	9 6	Con trol	
				5/ 2	425	0 61	0 61		0 49	0 44	1 92	1 92	0 092	0 092	0 093	0 23	0 23	0 23	0 23	6 4	6 9	6 9		
7	36	M	2	9/ 1	700	0 67	2 77	1 405	0 66	0 36	0 51	1 89	1 62	1 23	0 23	0 20	0 20	0 492	6 4	6 4	6 4	Portal cirrhosis with ascites		
				9/ 2	1,200	3 02	3 02		0 444	2 26	1 51	1 17	1 17	1 51	1 17	1 17	1 17	1 17	1 17	1 17	1 17		1 17	1 17
1	48	F	2	9/ 4	700	2 02	2 02		0 728	0 413	1 94	1 94	1 62	1 02	1 02	0 23	0 20	0 210	0 210	0 210	0 210	0 210	Chronic nephro sis	
				5/22	1,150	0 67	4 32	1 405	0 66	0 322	0 51	2 76	1 62	1 43	0 23	0 018	0 20	0 061	0 288	3 76	6 4	6 4		
				5/23	1,800	5 40	5 40		0 486	0 486	3 98	1 78	1 78	1 78	0 015	0 074	0 074	0 738	5 73	7 5	7 5			
				5/24	1,850	5 84	5 84		0 229	0 420	2 77	1 52	1 52	1 52	0 009	0 074	0 074	0 352	4 83	6 3	6 3			
				5/25	1,200	3 67	3 67		0 341	0 396	1 24	1 24	1 24	1 24	0 011	0 052	0 052	0 214	3 36	6 1	6 1			
				5/26	1,200	3 61	3 61		0 312	0 432	2 22	1 36	1 36	1 36	0 017	0 048	0 048	0 240	3 53	6 3	6 3			
				5/27	950	3 20	3 20		0 391	0 390	2 15	1 18	1 18	1 18	0 011	0 036	0 036	0 257	2 22	5 2	5 2			
5/28	1,050	2 70	2 70		0 311	0 420	1 94	1 23	1 23	1 23	0 011	0 041	0 041	0 284	3 15	5 9	5 9							

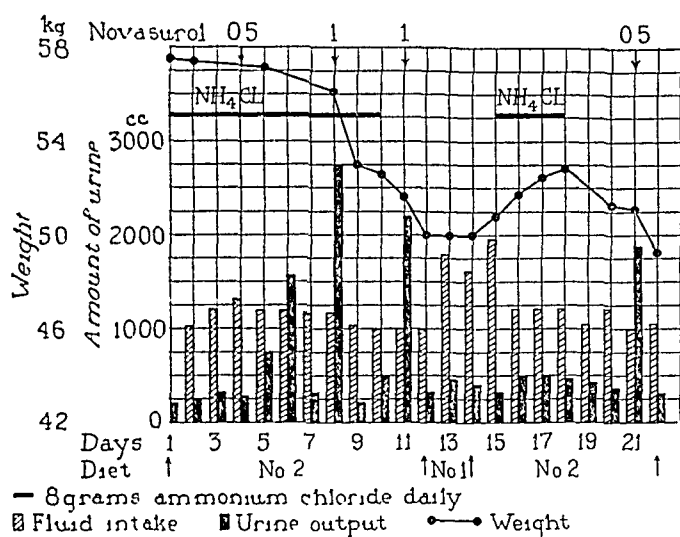


Chart 3 (case 3) — Findings in chronic nephrosis

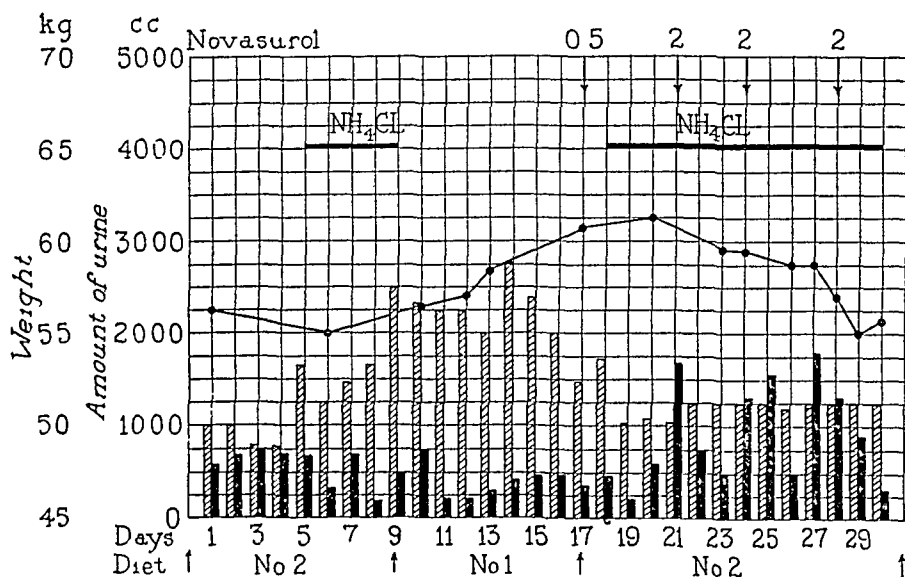


Chart 4 (case 4) — Findings in polycythemia with ascites heavy horizontal line, from 36 to 72 Gm of ammonium chloride, curve, weight, shaded columns, fluid intake, solid columns, urine output

taneous diuresis and loss of edema occurred and body weight decreased 8.5 Kg on the diet alone. Later it was found necessary to use novasurol and ammonium chloride to reduce the marked edema further. Similarly, in a case of Banti's disease with ascites the patient lost 2 Kg in body weight in seven days on the diet alone (chart 2).

Two patients undergoing the combined treatment found this diet difficult to take so the salt and water content was increased, there was a rapid retention of fluid and gain in weight. One of these, a patient with chronic nephrosis (case 3, chart 3), was finally able to take the low salt, low fluid diet regularly and the combined treatment produced the desired effects. We had a similar experience in a case of ascites (case 4, chart 4).

Several of our patients have found it necessary to remain on this diet for a period of three months and no ill effects have been noted. The patients' adherence to the diet is of interest for they soon realize from experience that if the intake of water and salt is increased beyond their tolerance an increased retention of fluid and a gain in weight occurs.

SUMMARY

Carefully controlled diets of low mineral and water content are both practicable and effective in the treatment of cases of edema and ascites. The diets may be varied in protein and caloric value with little increase in mineral or water content.⁴ There have been no demonstrable ill effects from the continued use of these diets.

⁴ Atwater, W. O., and Bryant, A. P. *The Chemical Composition of American Food Materials*, ed. 3, United States Department of Agriculture, Office of Experimental Station, Bull. 28, Washington, Government Printing Office, 1906.

WATER METABOLISM

II FURTHER OBSERVATIONS ¹

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In a previous article ¹ it was reported that the amount of water that it was possible to cause a dog to excrete by the intravenous injection of glucose was directly proportional to the alkalinity of the blood as measured by the carbon dioxide combining power of the plasma (Van Slyke). The level of carbon dioxide of 45 is the critical point and if the dog is below that level of alkalinity, dehydration by glucose injections is impossible, all the water being "fixed" by the colloids or at least being in a relatively firm combination with the colloids. Above that level, an increasingly large amount is held in a freer or looser combination, and this "free" water acts as a body reserve.

A continuation of these studies using hypertonic salt solution as the dehydrating agent, has yielded similar results. Dogs were injected intravenously with a 5 per cent solution of sodium chloride at the rate of 25 cc per kilogram. The injections were made with a Woodyatt pump and planned to consume ninety minutes. A catheter was introduced into the dog's bladder and the flow of urine measured. In this set of experiments the onset of the diuresis was less prompt than in the previously reported glucose dehydrations. The injections were continued for from seventy to ninety minutes before the urine excreted exceeded the water injected. The length of time before the flow of urine ceased was from three and a half to four hours. In general sodium chloride proved to be a more powerful diuretic than glucose. In other words it was possible to win water from the tissues at lower levels of alkalinity. This is in line with our knowledge of the behavior of colloid-water combinations in vitro. The experiment given in table 1 is illustrative of the method.

If the results of the previously reported glucose dehydrations are plotted the curve of chart 1 results. It will be noticed that the results are not strictly quantitative. This is undoubtedly owing to the fact that the sugar metabolism of the dog is not a constant factor. Slight variations in the glycogen reserve of the liver, in the general nutrition of the animal, as well as the functional capacity of the pancreas have just enough influence to make the curve slightly irregular.

¹ From the department of surgery, University of Illinois College of Medicine.

In these salt solution dehydrations, I was quite astonished when plotting the curve to note that when the points were laid on the chart it was possible to draw a line through them with a ruler. In this case no metabolic elements entered into the equation. The mathematical accuracy of the results can be interpreted only as a confirmation of the theory that in these water problems we are dealing solely with physico-chemical forces, and that no "vital" or "life" factors are acting. The results are comparable in accuracy with those achieved in ordinary chemical work on colloids.

TABLE 1—*Experiment 36*

Male dog, weighing 9 Kg, injected with 330 cc of 5 per cent sodium chloride at a constant rate during ninety minutes, carbon dioxide, 46.7

Time	Intake	Output	Loss	Loss per Kg
10 35 injection begun				
10 50	55	10		
11 05	110	70		
11 20	165	140		
11 35	220	220		
11 50	275	320	45	4
12 05 injection stopped	330	520	190	21
12 20	330	600	270	30
12 35	330	650	320	35
1 05	330	680	350	39
1 15	330	700	370	41
1 30	330	720	390	43
2 00	330	735	405	45

This dog, therefore, whose carbon dioxide was 46.7 was dehydrated to the extent of 45 cc per kilogram.

Table 2 shows the results of a series of such experiments.

TABLE 2—*Results in Series of Experiments*

Experiment	Carbon Dioxide	pH	Water Loss
40	53.0	7.45	40
43	52.4	7.40	42
28	49.4		60
32	48.0		55
29	47.5		50
36	46.7		45
38	44.3	7.40	36
30	42.3		26
34	40.8		22
42	36.8	7.25	4.5

It will be noted that in each curve there is a drop in the amount of free water as we reach the extreme alkaline end of the scale. This is also strictly in line with our knowledge of the behavior of proteins in vitro.

Hydrogen ion estimations (table 2) were made in some cases and were found to run parallel in a general way. The method used (colorimetric) is not accurate enough to fall within the margin of error in these studies and therefore no exact correspondence is to be expected.

CONCLUSIONS

1 The amount of "free" water in the tissues varies with the alkalinity of the blood as measured by the carbon dioxide combining power of the plasma

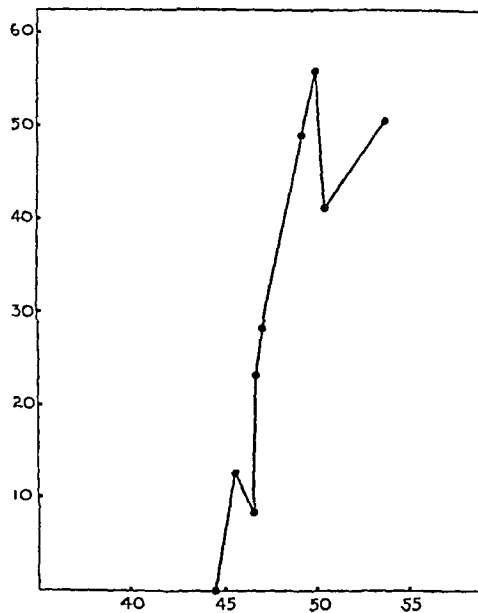


Chart 1—Glucose dehydrations abscissas, cubic centimeters of water lost, ordinates, carbon dioxide (Van Slyke)

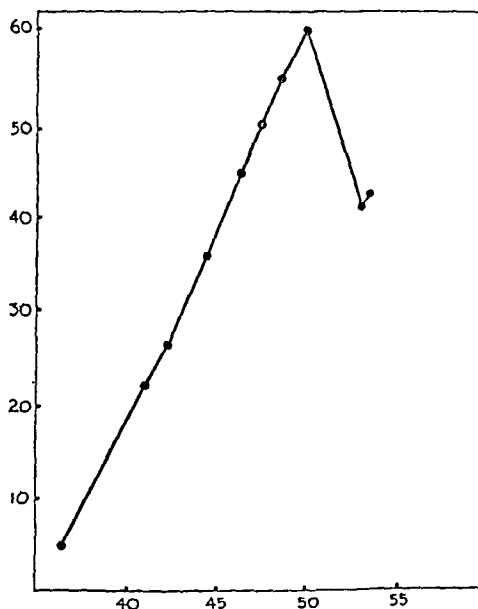


Chart 2—Salt solution dehydrations abscissas, cubic centimeters of water lost, ordinates, carbon dioxide (Van Slyke)

2 The exact mathematical accuracy of this proportion, when hyper-tonic salt solution is used as the dehydrating agent, is evidence that the elimination of water in these experiments is purely a physicochemical phenomenon and that no "vital" factors need be considered

THE EFFECT OF DIGITALIS ON VENTRICULAR PREMATURE CONTRACTIONS *

HAROLD L OTTO, M D

AND

HARRY GOLD, M D

NEW YORK

In a recent article by one of us¹ attention is called to the errors arising from theoretic deductions on the effect of digitalis in disorders of cardiac rhythm. Without a more exact understanding of the precise manner in which digitalis in varying doses affects the different cardiac functions, and also without a clearer understanding of the precise mechanism producing the different disorders of rhythm, it is necessary, in order to ascertain the response to digitalis, to investigate each arrhythmia directly. It is a matter of common experience to observe premature contractions, particularly of the ventricular type, called forth by digitalis. The ventricular premature contraction is especially common in patients with auricular fibrillation. In some of the latter, large doses are necessary, in others, rather small doses are sufficient to produce them.

Our knowledge of the effect of digitalis on premature contractions occurring spontaneously is not quite so definite. In 1911 Edens² recorded the impression that the behavior of premature contractions toward digitalis depends on the cause that produces them. Thus he found that in a patient with premature contractions during the course of an attack of acute rheumatic fever digitalis had no effect. Likewise, in patients in whom smoking was the etiologic factor digitalis was without influence on the frequency of the premature contractions. However, he stated that he observed digitalis influenced favorably a tendency to the production of premature contractions in a number of patients with both normal and decompensated hearts. Wenckebach³ stated that he cured (?) a number of patients with troublesome premature contractions in diseased as well as in perfectly healthy hearts by "very small doses of digitalis only." He explained the effect of the

* From the third (New York University) medical division and adult cardiac clinic of Bellevue Hospital, and the department of pharmacology, Cornell University Medical College.

1 Gold, H. Action of Digitalis in the Presence of Coronary Obstruction, *Arch Int Med* **35** 482 (April) 1925.

2 Edens, E. Ueber Digitaliswirkung, *Deutsches Arch f klin Med* **104** 512, 1911.

3 Wenckebach, K. F. The Effects of Digitalis on the Human Heart, *Brit M J* **2** 1600, 1910.

small dose as a depression of the irritability of the myocardium contrary to the effect of large doses that increase the irritability of the myocardium and give rise to premature contractions. Edens and Huber⁴ reported a case of bigeminy of the auricular type with a normal basic rhythm in which a regular rhythm followed the administration of digitalis. They were able to find only two other cases in the literature, one, reported by Wenckebach, of the ventricular type, and the other, reported by Hering, of a character not determined. Mackenzie⁵ believed that the cessation of premature contractions under digitalis was independent of the drug and that when the premature contractions had persisted for months or years no form of treatment seemed to abolish them. Christian⁶ stated that the relation of digitalis to premature contractions was not established and added that their presence could be neglected in considering the probable efficiency of digitalis therapy.

It is obvious that the few clinical observations recorded on the effect of digitalis on premature contractions are contradictory and, on the whole, unsatisfactory. This is probably due in part to the inherent difficulties attending a thorough investigation of the subject. Premature contractions frequently occur in patients whose hearts are otherwise normal. These patients do not ordinarily apply for treatment, and when they do they are rarely kept in the hospital for the length of time necessary to control properly their reaction to the drug. Furthermore, premature contractions occurring spontaneously show considerable variation in their frequency in the same patient at different times during the day and under different conditions, and for intervals of days or weeks may disappear without any treatment. This inconstancy necessitates long periods of control, the absence of which in the records of most of the earlier experiments has rendered the evidence inconclusive.

For some time we have been pursuing a study of the effects of various drugs on premature contractions. In the course of our work we have been able to complete observations on one patient with premature contractions the results of which answer conclusively a question to which there has not been a definite answer in the literature. Whereas it is known that in some patients large doses of digitalis can produce premature contractions of ventricular origin, can large doses cause the disappearance of premature contractions occurring spontaneously? This article is a report of the method employed and the results obtained in the observations on this patient relevant to this question.

4 Edens, E., and Huber, J. E. Ueber Digitalisbigeminie, *Deutsches Arch f. klin. Med.* **118** 476, 1916.

5 Mackenzie, J. *Diseases of the Heart*, 1913, p. 202.

6 Christian, H. A. The Use of Digitalis in Various Forms of Cardiac Arrhythmia, *Boston M. & S. J.* **173** 306, 1915.

REPORT OF CASE

History—A man, aged 56, a brass finisher by trade, had had no childhood diseases except measles. He had had rheumatism at the age of 43. He stated that he had had no venereal diseases. The bowels were regular. He had smoked three pipes daily for the last twenty years and took two cups of coffee daily but no tea. Before prohibition he occasionally drank whisky and was intoxicated about once a year. He had not noticed any relation between his present complaints and his smoking, coffee or alcohol. In the previous three years he had been treated several times for sleeplessness and palpitation. Nervousness always aggravated the symptoms. He came to the clinic because of a "jumping heart," dull pain in the precordium and sleeplessness.

Physical Examination—The patient was well nourished, weighing 160 pounds (72.6 Kg). There was no evidence of infection from teeth or tonsils. The lungs were negative. The abdomen was negative, the liver and spleen were not palpable. There was moderate sclerosis of the brachial and temporal arteries. There was no edema. The apex beat was visible and palpable in the fifth space, 11 cm. from the midline. The sounds were of good quality. There was considerable accentuation of the second aortic sound. There were no murmurs. The ventricular rate was from 70 to 80 per minute with a pulse deficit of from 10 to 15 beats. The electrocardiogram showed a basic sinus rhythm interrupted by frequent premature ventricular contractions. The temperature was normal. The urine and the blood were normal. The blood pressure varied from 200 systolic, 120 diastolic to 190 systolic, 90 diastolic.

The diagnosis was arteriosclerosis, hypertension, enlarged heart and premature contractions.

Treatment—The patient was admitted to the hospital and put to bed. Electrocardiograms of five minutes' duration on a preferred lead (Lead I in this case) were taken on bromide paper three times daily, at approximately 9 a. m., 1 and 5 p. m. On days of rapid digitalization these electrocardiograms were taken every hour during the day. When, as occasionally happened, electrocardiography was not available, the ventricular rate was counted for 500 consecutive beats, the premature contractions being recorded as they occurred. After the twenty-seventh day of observation the patient was discharged from the hospital and one such tracing was taken three times a week to keep record of the prevailing rhythm and number of premature contractions. On occasions of repetition of full digitalization three records were taken the day before, a record every two hours on the day of administration, and three records the day following the administration of the digitalis.

Analysis of Chart—The results obtained are given in the accompanying chart. Curve B is plotted from the average number of premature contractions per minute of each record. It shows clearly the extraordinary variations in the number of premature contractions at different times of the same day and of different days. For instance, at noon of the second day there were eighteen premature beats per minute, whereas at 5 p. m. of the same day there were only four premature beats per minute. Had any drug been administered in the morning one could easily have fallen into the error of assuming it to be the cause of the marked reduction in the number of premature beats.

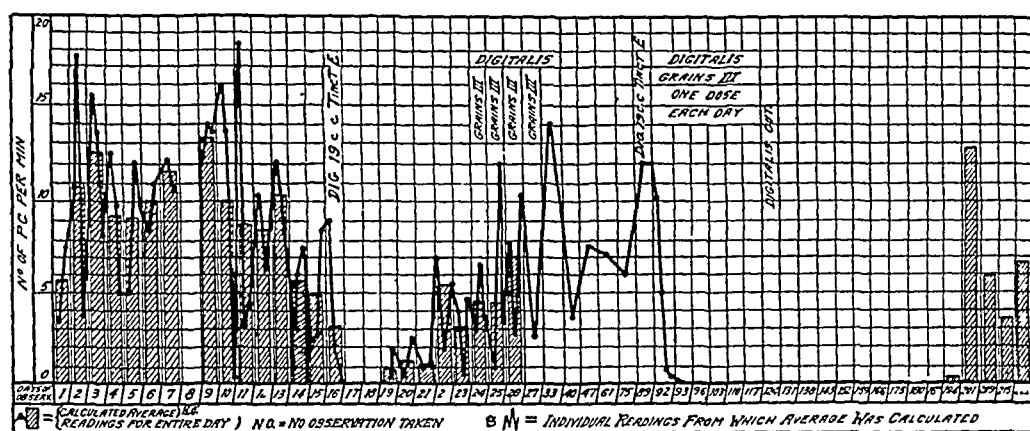
The shaded areas, A, of the chart indicate the calculated average number of premature beats per minute for each day, based on the three daily electrocardiograms.

The first control period lasted fifteen days with the premature contractions ranging between five and thirteen per minute daily. On the sixteenth day, 19 cc of tincture of digitalis with a strength of 1 cc to the cat unit was given by mouth in one dose at 9:30 a. m. after the first electrocardiogram was taken. The curve shows the continuous diminution in the number of premature contractions during the day. Five hours after this full dose of digitalis the electrocardiogram

showed no premature contractions for the first time in fifteen days of observation, during which period forty-five electrocardiograms of five minutes each were taken

For two days following the first full dose there were no premature beats. They began to reappear in small numbers on the third day (day 19). Eight days after the first full dose, 3 grains (0.19 Gm) daily of the powdered digitalis leaf was administered for four days. These smaller doses of digitalis failed to abolish the premature beats. However, from the time of the digitalis administration the number of premature beats was considerably less than for any similar period previously.

Then for a period of fifty-nine days (from day 33 to day 92) no digitalis was given. The premature contractions returned practically to the same range as in the first control period, from four to fourteen per minute daily. On day 92 the patient again received 19 cc of the same tincture of digitalis employed previously. The number of premature beats began to diminish gradually and seven hours after this full dose of digitalis they had completely disappeared.



Results of treatment

For the period of thirty-one days following this full dose, the patient received 3 grains daily of the powdered digitalis leaf. Throughout this period the premature contractions were absent. On day 124 the drug was again discontinued, the premature beats reappearing on day 194, or 69 days after the drug had been withdrawn.

COMMENT

In the case presented digitalis in full doses given at once completely abolished spontaneously occurring premature ventricular contractions. Three grains daily of the powdered leaf for four days failed to abolish them. They disappeared after a full dose in the time necessary for practically complete absorption of the drug. The same results were obtained on repetition. After the first full digitalization, seven days were allowed without digitalis for elimination of the drug, the premature contractions began to reappear on the third day. However, when a daily maintenance dose of 3 grains (0.19 Gm) of the leaf was started immediately after the second full digitalization, the premature contractions did not reappear. The persistence of the effect after withdrawal of the digitalis was considerably longer following prolonged digitalization than after a single full dose.

Since there was no evidence of circulatory failure in this patient the disappearance of the premature contractions was not accompanied by any subjective or objective evidence of improved circulation. There was no change in the blood pressure. The annoying sensation of "jumping of the heart" disappeared in the absence of the premature contractions.

PRESSURE ON THE CENTRAL NERVOUS SYSTEM IN ITS RELATION TO HYPERGLYCEMIA CHRONIC PIQÛRE¹

WIKTOR Z TYCHOWSKI, M D

AND

CAROLINE CROWELL

PHILADELPHIA

Claude Bernard's piqûre¹ showing the close relation of the central nervous system to carbohydrate metabolism attracted the attention of many investigators and clinicians, so that cases of transient glycosuria as well as even cases of diabetes mellitus were examined for changes in the central nervous system. Since it was found that cases of tumors of the central nervous system and also cases of recent cerebral and subdural (intracranial) hemorrhages are often associated with glycosuria, special attention was paid to cases showing symptoms of direct pressure on the medulla oblongata. Indeed, tumors of its own or neighboring tissues, blood extravasations in its immediate vicinity or even into the fourth ventricle, and echinococcus situated occasionally in the cavity of the fourth ventricle have furnished useful anatomopathologic material, suggesting strongly a possible interrelationship between the glycosuria and the pathologic findings in or near the medulla.

The accompanying table includes the cases compiled from the meager literature on this subject. Since blood sugar, the subject under investigation in the present work, has been analyzed in pertinent cases only by recent workers, the table also contains those cases, taken chiefly from old publications, in which the urine only was examined for sugar content. This seems justifiable since, with few exceptions, glycosuria is secondary to a primary hyperglycemia. There also are added a few cases in which the sugar content of the cerebrospinal fluid has been estimated and a hyperglycorrhachia reported. A relation between the sugar level of blood and cerebrospinal fluid has been suggested and demonstrated on clinical material by Thalhimer and Updegraff,² the same point of view is upheld by Dopter³ and by Polonovski and Duhot.⁴ Moates and Keegan,⁵ experimenting on cerebrospinal

From the department of physiology, University of Pennsylvania

1 Bernard. *Leçons de Physiologie Experimentale*, Paris, 1855, p 309

2 Thalhimer, W, and Updegraff, H. Sugar Content of Blood and Spinal Fluid in Encephalitis, *Arch Neurol & Psychiat* 8 15 (July) 1922

3 Dopter, C. *Bull Acad de med* 83 203 (March 2) 1920

4 Polonovsky, M, and Duhot, E. *Presse med* 31 157, 1923

5 Moates, G H, and Keegan, J J. *J Lab & Clin Med* 8 825-828 (Sept) 1923

fluid, reported that the elevation of sugar level, which is known to occur in blood following ether anesthesia, is similarly present in cerebrospinal fluid. They do not, however, suggest any dependency of one sugar level on the other. Recently, Kasahara and Uetani⁶ demonstrated a decrease in the reducing power of cerebrospinal fluid following the injection of insulin. They interpret this as proof of the existence of an interrelationship between hyperglycemia and hyperglycorrhachia. The normal sugar value for human cerebrospinal fluid is from 0.04 to 0.068 per cent according to Moates and Keegan⁵ and from 0.048 to 0.07 per cent according to Mestrezat.⁷ In one case of cerebellar hemorrhage (Case 41 in table) the blood sugar was not estimated but that in the cerebrospinal fluid reached 0.117 per cent. In another case (Case 3, a patient with cerebral tumor) both hyperglycorrhachia and hyperglycemia were reported. Consequently in the table, previous figures in the literature are compiled and no distinction is made between results obtained from blood, cerebrospinal fluid or urine examination.

Cases from the Literature

Case	Lesion	Sugar, per Cent			Author and Remarks
		Blood	Cerebrospinal Fluid	Urine	
1	Tumor cerebri	0.237			Liefmann and Stern ⁸
2	Tumor cerebri	0.03			Oehlecker ⁹ , tumor slow growing
3	Tumor cerebri	0.158	0.079		Thalhimer and Updegraff ²
4	Tumor cerebri		0.042		Moates and Keegan ⁵
5	Haemorrhagia cerebri	0.150			Leire ¹⁰
6	Haemorrhagia cerebri	0.14			Kahler ¹¹ , estimation 3 days after onset
7	Haemorrhagia cerebri	0.16			Kahler ¹¹ , 10 days after onset
8	Haemorrhagia cerebri	0.11			Kahler ¹¹ , few days after onset
9	Haemorrhagia cerebri	0.12			Kahler ¹¹ , 8 days after onset
10	Haemorrhagia cerebri	0.10			Kahler ¹¹ , 16 days after onset
11	Haemorrhagia cerebri	0.13			Kahler ¹¹ , 3 days after onset, 10 days after onset 0.10 per cent
12	Haemorrhagia cerebri	0.33			Kahler ¹¹ , 2 months after onset, diabetes
13	Haemorrhagia cerebri	0.14			Kahler ¹¹ , 4 days after onset
14	Haemorrhagia cerebri	0.150			Feinblatt ¹²
15	Haemorrhagia cerebri	0.150			Feinblatt ¹²
16	Haemorrhagia cerebri	0.150			Feinblatt ¹²
17	Haemorrhagia cerebri			4.0	Frerichs ¹³
18	Haemorrhagia cerebri			1.08	Frerichs ¹³
19	Haemorrhagia cerebri			++	Frerichs ¹³
20	Haemorrhagia cerebri			0.5	Frerichs ¹³ , blood in all ventricles
21	Haemorrhagia cerebri			0.8	Frerichs ¹³ , blood in ventricles, pancreas unchanged
22	Haemorrhagia cerebri			1.0	Gradwohl ¹⁴
23	Haemorrhagia cerebri			3.0	Gradwohl ¹⁴ , blood clot in fourth ventricle

6 Kasahara, M., and Uetani, E. *J Biol Chem* **59** 433-436 (March) 1924

7 Mestrezat, W. *Presse med* **31** 157 (Feb 17) 1923

8 Liefmann and Stern. *Biochem Ztschr* **1** 299-308, 1906

9 Oehlecker. *Verhandl d deutsch Gesellsch f Chir* 1922, pp 491-511

10 Leire, cited by Bang, I. *Der Blutzucker*, Wiesbaden, 1913, p 123

11 Kahler, H. *Wien Arch f inn Med* **4** 129-148 (April) 1922

12 Feinblatt, H. M. *J Lab & Clin Med* **8** 500-505 (May) 1923

13 Frerichs. *Ueber den Diabetes*, Berlin, Hirschwald, 1884

14 Gradwohl. *M Rev* **40** 61-64, 1899

15 Gradwohl. *Philadelphia M J*, 1899, cited from Gradwohl (Footnote 14)

Cases from the Literature—Continued

Case	Lesion	Sugar, per Cent		Author and Remarks
		Blood	Cerebro spinal Fluid Urine	
24	Apoplexia	0 308		Hollinger ¹⁰
25	Apoplexia	0 219		Hollinger ¹⁰
26	Apoplexia	0 123		Hollinger ¹⁰
27	Apoplexia	0 09		Kahler ¹¹ , 1 year before apoplexia, few days before analysis slight attack
28	Apoplexia		0 69	Frerichs ¹³ , blood in all ventricles
29	Apoplexia		0 50	Frerichs ¹³ , polarimetric analysis
30	Apoplexia		0 8	Frerichs ¹³ , third and fourth ventricles filled with blood
31	Apoplexia		0 69	Frerichs ¹³ , blood in all ventricles, pancreas unchanged
32	Apoplexia		1 08	Frerichs ¹³ , liquid blood in all ventricles, pancreas unchanged
33	Apoplexia		2 95	Schuetz ¹⁷ , polarimetric estimation, 14 months later another attack with 24 per cent urine sugar, period between the two attacks sugar-free urine
34	Apoplexia		0 22	Loeb ¹⁸
35	Apoplexia		0 4	Loeb ¹⁸
36	Apoplexia		++	Ollivier ¹⁰ , sugar appeared 1 hour after onset and disappeared within 7 hours
37	Apoplexia		++	Ollivier ¹⁰ , sugar appeared 1½ hours after onset and disappeared in about 7 hours
38	Edema cerebri		0 2	Gradwohl ¹⁴ , sugar in urine for 3 days, Bremer's blood test positive until fifth day
39	Echinococcus cerebri	0 12		Oehlecker ⁹
40	Echinococcus basis cerebri	0 12		Oehlecker ⁹
41	Haemorrhagia cerebelli		0 117	Moates and Keegan ⁵
42	Haemorrhagia pontis	0 15		Kahler ¹¹ , 2 days after onset
43	Haemorrhagia pontis	0 13		Kahler ¹¹ , 3 days after onset
44	Haemorrhagia pontis	0 12		Kahler ¹¹ , slight attack 14 days before analysis
45	Haemorrhagia pontis et medullae oblongatae		++	Parkes ²⁰ , blood clot encircling the medulla, urine examined postmortem
46	Haemorrhagia pontis et ventriculi quarti		++	Markwordt ²¹ , urine examined postmortem
47	Tumor medullae oblongatae		++	Reimer ²² , tumor growing into fourth ventricle
48	Tumor tbc medullae oblongatae		6 0	De Jonge ²³
49	Tumor sarcoma medullae oblongatae		6 0	Dompeling ²⁴
50	Tumor plexus choroidei ventriculi quarti		++	Levrat-Perroton ²⁵
51	Tumor plexus choroidei ventriculi quarti		5 0- 8 0	Von Recklinghausen ²⁶
52	Haemorrhagia ventriculi quarti		2 0	Gradwohl ¹⁴ , Bremer's blood test positive
53	Cysticercus ventriculi quarti		++	Alt ²⁷ , patient showed periodic glycosuria
54	Cysticercus ventriculi quarti		2 5	Michael ²⁸

16 Hollinger, A Biochem Ztschr **17** 1-12, 1909

17 Schuetz Prag med Wchnschr **50** 613-615, 1892

18 Loeb Prag med Wchnschr **50** 615-616, 1892

19 Ollivier Gaz Hebdomadaire de med **11** 164-167, 1875

20 Parkes Lancet **2** 149-150, 1860

21 Markwordt Arch f klin Med **18** 111, 1876

22 Reimer Jahrb f Kinderheilkunde, 1876, pp 306-308

23 De Jonge Arch f Psychiat **13** 658-670, 1882

24 Dompeling Nederl Arch v geneesk **4** 179-190, 1869

25 Levrat-Perroton These, Paris, 1859, cited by de Jonge (Footnote 23)

26 Von Recklinghausen Arch f path Anat **30** 360-376, 1864

27 Alt Neurologisches Zentralblatt, 1902, p 567

28 Michael Deutsch Arch f klin Med **44** 597-604, 1889

Only a few cases can be found in the literature in which there was compression limited to the medulla oblongata and in which the sugar content either of blood or of urine was examined. Weber's²⁹ case of a tumor of the roof of the fourth ventricle of the brain was accompanied by glycosuria (3 per cent), but was complicated by fibrous changes in the pancreas. Osler³⁰ observed a woman with cysticercus in the fourth ventricle, but this case was complicated by the presence of diabetes mellitus. Michael²⁸ described another case of cysticercus of the fourth ventricle in which there was 2.5 per cent sugar in the urine. But the most interesting instance of this type is a patient, observed by Alt,²⁷ who showed a periodical glycosuria in which there may have been a causative connection between the local pressure exerted at certain times by the cyst on the medulla oblongata and this periodicity of the glycosuria. Other cases, shown in the table, in which mechanical compression of the medulla seems to have been probable (Cases 45 to 54) were all accompanied by glycosuria.

Besides these clinical findings on human beings affected with lesions of the central nervous system, there have been certain observations made during experiments on blood sugar in decerebrate animals³¹ which seemed to indicate an importance in hyperglycemia of mechanical stimulation of the persistent part of the central nervous system. Some decerebrated animals showed marked symptoms of medullary stimulation, especially slow and deep breathing, necropsy of these animals usually showed a blood clot lying on the ventral surface of the medulla oblongata. Frequent analyses of their blood gave sugar figures not only far above normal average values but also above figures obtained from animals similarly operated on but without hemorrhage.

On the basis of the foregoing collected findings the present work has attempted to decide

1 Whether mechanical compression of the medulla oblongata, acting without injury to its nervous tissue, causes carbohydrate mobilization

2 Whether an increase of cerebrospinal fluid pressure acting on the whole central nervous system gives the same result, i. e., a hyperglycemia

METHODS USED AND CONTROL OBSERVATIONS

Two chief series of experiments were devised to meet these problems. To create mechanical compression of the medulla, small amounts of paraffin or blood were injected into the cisterna magna, in both

29 Weber. *Internat. Clinics* 4: 78-87, 1921.

30 Osler, cited by H. Fernblatt (Footnote 12).

31 Bazett, H. C., Tychowski and Crowell. *Proc. Soc. Exper. Biol. & Med.* 22: 39-42, 1924.

cases the substance introduced acted simply as a foreign body. An increase of cerebrospinal fluid pressure was obtained by continuous injections of fluid into the cavum subarachnoidale. Sugar variations were followed by frequent blood analyses.

Animals Used and Their Treatment During Experiments—Cats were used in all experiments. To avoid active digestion and emotional processes the animal was isolated and made to fast from sixteen to twenty-four hours before the beginning of the experiment. No previous special diet was provided.

The anesthetized animal was placed on a specially heated table and its position was not disturbed throughout the experiment. By the intermittent use of the heating apparatus an approximately constant rectal temperature was maintained, otherwise the temperature tended to fall during the first two or three hours.

Anesthesia—The effect on blood sugar of a great number of anesthetics is well established. Particularly chloroform and ether elevate the sugar to so high a level that any changes at this level are difficult to interpret. It was therefore necessary to use only such anesthetics as do not of themselves cause hyperglycemia, further, these had to assure prolonged and uniform anesthesia when given in sufficient amount at the beginning of an experiment. Hypnotics rather than anesthetics give such results.

Three drugs were used: (1) chlorbutanol (trichlor-tertiary-butyl alcohol), (2) iso-amyl-ethyl barbituric acid, (3) barbital sodium (sodium diethyl-barbituric acid), and (4) chloroform, for a few control experiments.

The first drug used was chlorbutanol. This, because of its insolubility in water, was kept in 12.5 per cent alcoholic solution. Measured amounts of this standard solution were diluted to 25 cc with warm water and administered through a stomach tube. The dosage was 0.17 Gm per kilogram of body weight. Thus, about 1 cc of alcohol per kilogram of body weight was given along with the anesthetic. Such an amount would not increase the blood's reducing power, rather would it diminish it, as shown by Blatherwick, Maxwell and Long³² in their experiments on rabbits, Fuller's³³ work on diabetic patients confirms in human beings these experimental findings. Some animals, probably as a result of the alcohol, became restless and excited before attaining complete anesthesia. This was reached in from about ten to twenty minutes. Corneal reflexes remained

³² Blatherwick, N. R., Maxwell, and Long, M. L. *Am J Physiol* **67** 346-347, 1923.

³³ Fuller, L. S. *J Metabolic Res* **1** 609-617 (May) 1922.

The second drug, iso-amyl-barbituric acid, has been investigated by Page,³⁴ who found it a satisfactory anesthetic and one with little or no influence on blood sugar. We used it in a few experiments in his doses (from 0.09 to 0.12 Gm per kilogram) with results that confirmed his work. Because of its insolubility the drug was first converted into sodium salt by tenth normal sodium hydroxid solution, after which it was given by stomach tube in 25 cc of water.

We used most often the last preparation, barbital sodium, a barbituric acid derivative recently investigated by Dox³⁵ and Ellis.³⁶ It is easily soluble in water and is of prolonged and uniform effect, from 0.25 to 0.35 Gm per kilogram of body weight, dissolved in 25 cc of water and given to a fasting animal by stomach tube, will produce a complete surgical anesthesia in from twenty to forty-five minutes which may last for days. Control experiments were made to test the effect of barbital

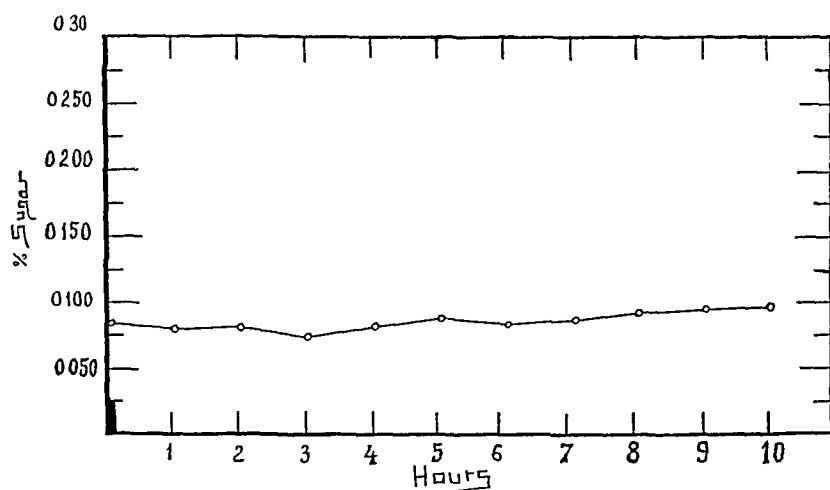


Fig 1—Effect of barbital sodium on blood sugar

sodium on blood sugar and gave negative results, except for an occasional slight decrease during the first two or three hours. Figure 1 shows such a control experiment.

A peculiar effect of the drug, noted in almost every experiment, was an irritation of the nasal mucous membranes, manifested by sneezing, there also was a dilatation of the small blood vessels of the ears and mucous membranes of the nose and mouth. Blood pressure records showed diverging systolic and diastolic levels though mean pressure was unchanged. The vessel dilatation usually disappeared after three or four hours.

A few experiments were performed under chloroform. We hoped that they would show that the same factors were effective even at high

34 Page, I. H. *J. Lab. & Clin. Med.* **9** 3, 1923.

35 Dox. *J. Am. Pharm. A.* **12** 602-609, 1923.

36 Ellis. *J. Pharm. & Exper. Therap.* **21** 323-342 (June) 1923.

sugar levels but the results were somewhat complicated. The chloroform was given through a trachea cannula. All connections were as short as possible, a screw clip altered the amount of admixed air and was adjusted so as to maintain a light anesthesia.

"Normal" Blood Sugar in Cats—There is no steady sugar level in blood, it changes continuously. Exertion affects it, so does body temperature, emotional disturbances and food intake, and in a larger sense the animal's nutrition is important because of its influence on available glycogen. These changes can all be kept within certain physiologic limits, however, if the proper anesthetic is used and the experiments standardized.³⁷

The literature on normal blood sugar in cats is conflicting. Scott³⁸ stated the normal average blood sugar in cats to be 0.069 per cent. Abderhalden³⁹ found in one analysis 0.0851 per cent. Pavy⁴⁰ obtained an average of 0.088 per cent from six estimations (cardiac blood). Boehm and Hoffmann⁴¹ from twenty-six estimations, including three animals fasted eight days, gave 0.15 per cent, with the limits of 0.11-0.31 per cent. Mellanby⁴² considers the normal content to be about 0.2 per cent and Rona and Takahashi,⁴³ using polarimetric methods on four animals, reported variations between 0.154 and 0.355 per cent, with an average of 0.28 per cent. Griffith⁴⁴ doubts the existence of a "normal" blood sugar value, pointing out individual variations, changes arising from simple handling of the animal before anesthetization, from anesthetics or from operations in the course of the experiments.

In spite of the foregoing divergent findings there must exist limits that the normal animal does not exceed. Many of the foregoing figures are often evidently too high, with a blood sugar of 0.3 per cent or even much lower, glycosuria appears, such values must therefore be considered as a hyperglycemia.

A number of standardized experiments were performed, without anesthesia, to define those limits for cats. The animals received their last meal twenty-four hours before the estimation and were isolated in a quiet room. Blood was taken from the ear by a quick cut with a sharp razor blade, while the assistant stroked the cat. No pain reaction was noted. The following figures were obtained: experiment 1, 0.076 per cent, experiment 2, 0.0625 per cent, experiment 3, 0.055 per cent, and experiment 4, 0.066 per cent.

37 Scott. *Am J Physiol* **45** 578, 1918.

38 Scott. *Am J Physiol* **34** 271, 1914.

39 Abderhalden. *Ztschr f physiol Chem* **25** 65-115, 1898.

40 Pavy. *J Physiol* **24** 479-517, 1899.

41 Boehm and Hoffmann. *Arch f Exper Path u Pharmacol* **8** 271-308, 1878.

42 Mellanby. *J Physiol* **53** 1 (Sept) 1919.

43 Rona and Takahashi. *Biochem Ztschr* **30** 99-106, 1911.

44 Griffith. *Am J Physiol* **64** 618, 1923.

In one case different treatment was used. The animal was operated on aseptically, the carotid was exposed and ligated and the skin resutured under the exposed vessel, thus about 1.5 cm. of the vessel remained outside. The operation, performed under chloroform, took only a few minutes. Twenty-four hours later blood taken from the exposed vessel showed a sugar content of 0.09 per cent. The first few cubic centimeters of blood were discarded so that only circulating blood was analyzed. No food had been taken since the operation. The rectal temperature at the time of sampling was 38.6 C.

The foregoing figures show that the basal blood sugar of fasting cats approaches the lower limit of the values given in the literature and varies between 0.055 and 0.09 per cent. These limits were used only as a rough basis. In this work one and usually two analyses were always made at the beginning of each experiment and sugar changes occurring during the experiment were compared with this initial level. Any animals with excessively high initial values (such as were often noted to accompany pathologic skin changes) were excluded from further work.

Method and Details of Sugar Estimation in Blood—Many investigators have shown that an acute anemia is always followed by hyperglycemia. Since in most of the experiments sugar estimations were made every half-hour and since many experiments took ten hours or more, it was necessary to choose a method requiring as little blood as possible, yet sufficiently exact. McLean's⁴⁵ method meets both demands, having the additional advantage of being titrimetric. The four hundredth normal sodium thiosulphate solution for this was freshly prepared at the beginning of every experiment and standardized against a known copper solution, which in turn had been checked against a known glucose solution. The errors of the method as tested with a standard glucose solution did not exceed 2 units in the third decimal place (± 0.002).

Blood from a clean cut incision of the animal's ear was collected on a paraffined watchglass and 0.2 cc. was taken at once into a micropipet and emptied into the sodium sulphate solution. Quick manipulation rendered any anticoagulant unnecessary. After deproteinization the analysis was in every case completed at once, thus avoiding the addition of antiseptics and excluding glycolysis.

RESULTS OBTAINED

1 *Mechanical Pressure on Medulla Oblongata*—(a) Injections of Paraffin into Cisterna Magna. In attempting to localize mechanical pressure to the medulla oblongata injections, both of paraffin and

⁴⁵ McLean. *Biochem J.* **13**, 135, 1919.

blood, were made through the occipito-atlantal space. In the first case a mixture of solid paraffin and paraffin oil was used, prepared in such proportion that the melting point lay between 34 and 37 C. Measured amounts of the mixture were injected at the temperature of 37 C.

Figure 2 shows the effect on blood sugar of such an injection.

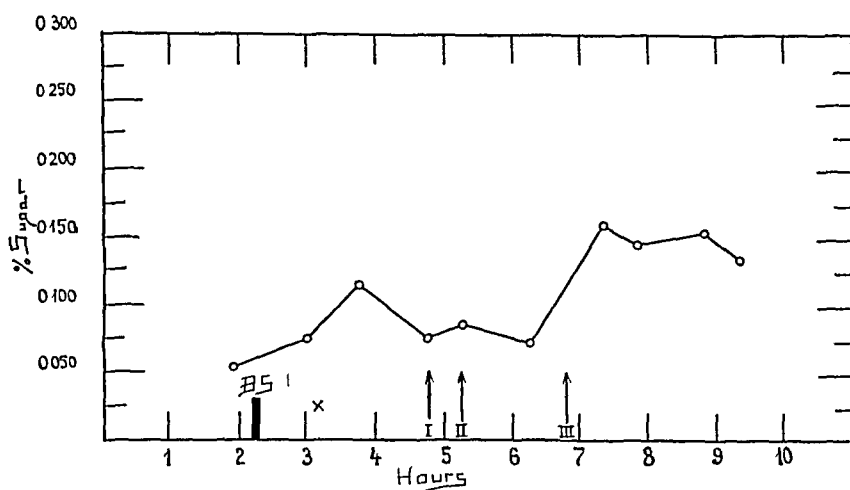


Fig 2—Effect on female cat, weighing 2,300 Gm, of barbital sodium anesthesia, BS, at X puncture of cisterna magna, three injections of 1 cc, 2 cc and 3 cc of paraffin are indicated by arrows.

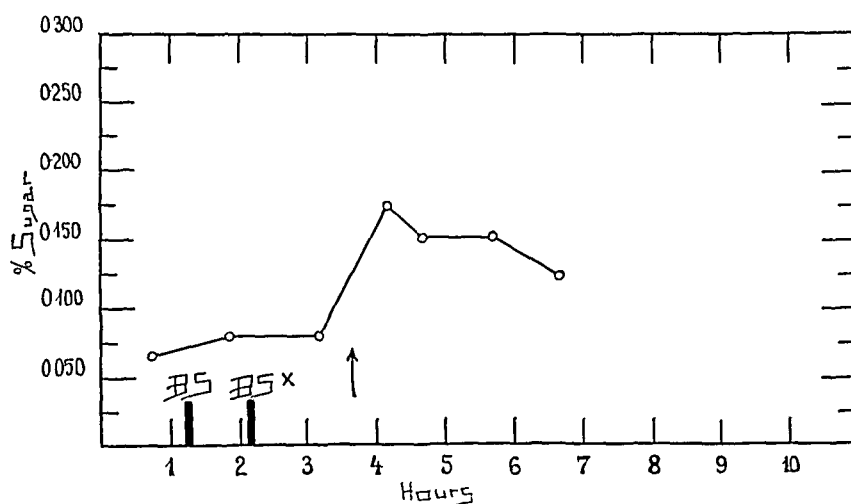


Fig 3—Effect on female cat, weighing 2,900 Gm, of barbital sodium anesthesia, at X puncture of cisterna magna, sixty minutes later injection of 15 cc of blood into cisterna magna, no change in respiration.

The first two injections produced no marked change in blood sugar, thirty minutes after the third injection the sugar content rose from 0.072 to 0.159 per cent. The last injection also caused a remarkable change in respiration, which even stopped for a few seconds, but soon returned to normal. The animal was killed with ether and its neck cooled by the external application of ether, care being taken not to dis-

turb the animal's position Necropsy then showed a paraffin clot covering the medulla oblongata with a slight amount going into the cavum cranii

(b) Injections of Blood into the Cisterna Magna The following experiments were devised to produce the conditions of an "artificial hemorrhage" About 2 cc of blood were taken from the ear of the cat

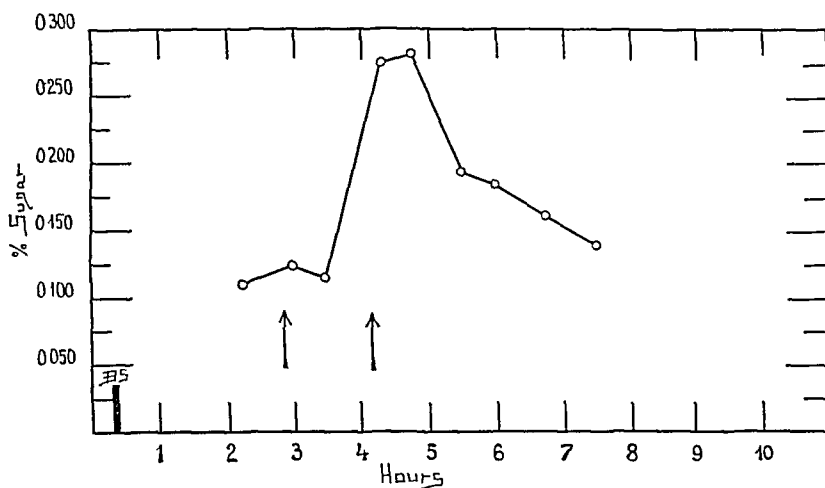


Fig 4—Effect on female cat, weighing 3,200 Gm, of barbital sodium anesthesia, at arrows injections of blood first injection 0.5 cc into muscles of neck, second, 1.9 cc into cisterna magna, after second injection respiration became slower and deeper, but soon returned to normal

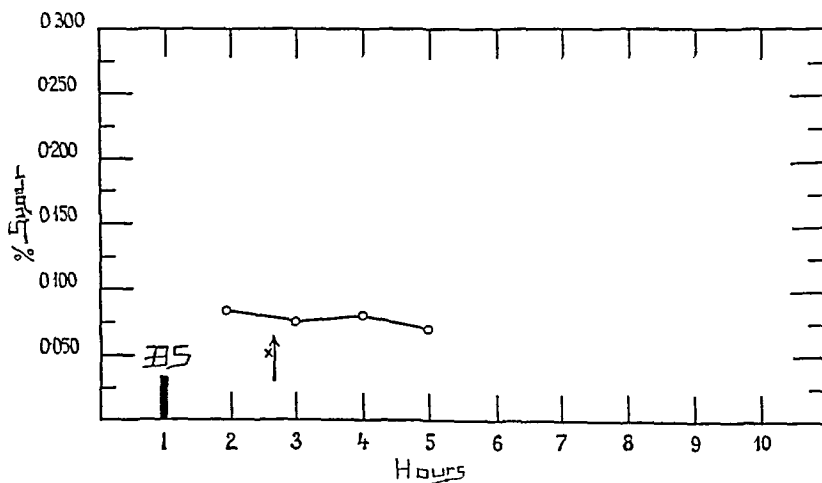


Fig 5—Effect on male cat, weighing 2,700 Gm, of barbital sodium anesthesia, at X puncture of cisterna magna, followed by slow (about one minute) injection of 0.5 cc of blood, no change in respiration, necropsy showed thin and elongated blood clot lying on lower left side of medulla oblongata

under experimentation Measured amounts were injected. Animals injected slowly showed no respiratory changes, those injected quickly behaved as in similar experiments with paraffin Figures 3 and 4 show the results of blood injections

In the experiment of which the data are given in Figure 3 the sugar content before and after puncture was 0.079 per cent, as against 0.174 per cent eighteen minutes after injection, in that of Figure 4 the first injection of 0.5 cc of blood was made into the muscles of the neck with a resultant rise of sugar from 0.109 to 0.124 per cent, the second injection into the cisterna magna was followed by a rise from 0.115 to 0.275 per cent. Since it is to be expected that the pressure exerted on the medulla oblongata will depend not only on the amount of blood injected but also on the rate of injection, several experiments were made, in which only comparatively small amounts of blood (from 0.5 to 1.1 cc) were injected slowly. Two experiments of this type are shown in Figures 5 and 6.

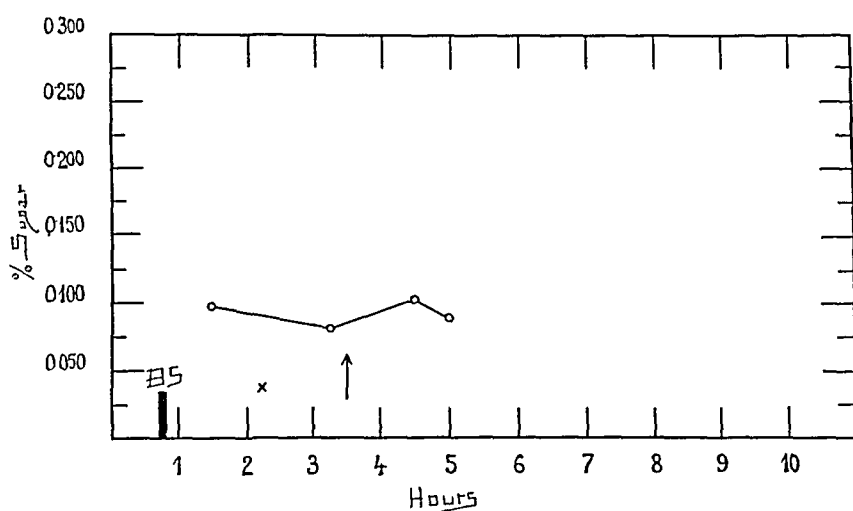


Fig. 6—Effect on male cat, weighing 3,000 Gm., of barbital sodium anesthesia, at X puncture of cisterna magna, at arrow injection of 1.1 cc of blood into cisterna magna.

Both the foregoing experiments were negative for the blood sugar was practically unchanged. This probably indicates that the mechanical agent is the only effective one, for other conditions in these experiments were the same as in the previous ones.

2 Hydrostatic Pressure on the Whole Central Nervous System—The next part of the work deals with the effect of artificially raising cerebrospinal fluid pressure over longer periods of time, this simulates certain pathologic conditions that are usually associated with hyperglycemia, hyperglycorrhachia and glycosuria, but in which there is no local mechanical pressure on the medulla oblongata. Cerebral tumors and hemorrhages distant from the medulla, meningitis, etc., cause commonly a rise of intracranial pressure which is transmitted throughout the craniospinal cavity by the incompressible cerebrospinal fluid.

Although Weed and Hughson⁴⁶ state that the cranium and the spinal column with their ligaments in an adult individual constitute, within physiologic limits, an inelastic, rigid container, this closed cavity does not represent a reservoir in which the pressure may be raised artificially and kept on a high level by means of a single injection of a certain amount of fluid. Rociński and one of us⁴⁷ showed in experiments on dogs and in clinical work on human subjects that such an

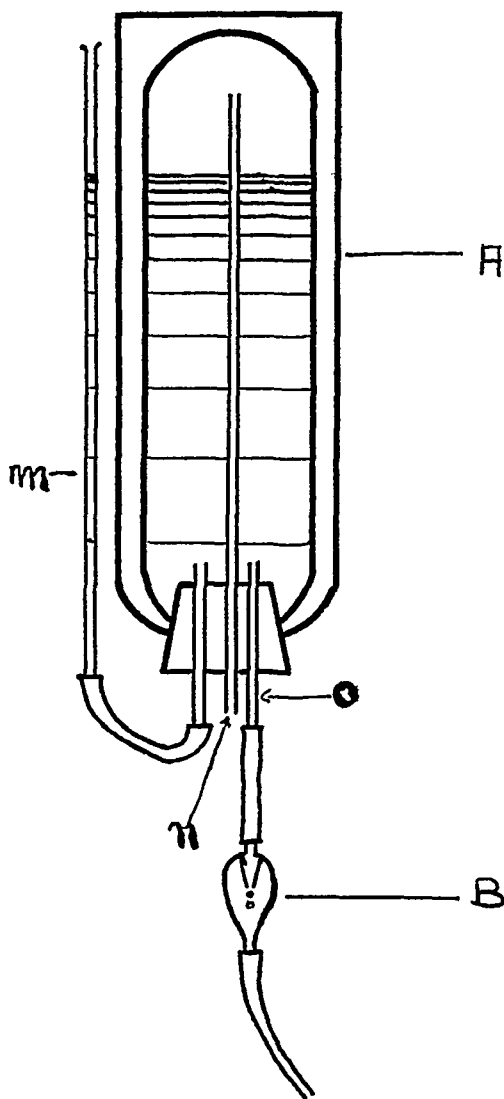


Fig 7—Saline reservoir

artificial rise of cerebrospinal fluid pressure, produced by a single injection of fluid into the subarachnoid space, lasts for a short time only, resorption is rapid enough to restore the initial pressure in a few minutes. To meet this difficulty in the present work a continuous injection

46 Weed, L. H., and Hughson, W. *Am J Physiol* **58** 85-100 (Nov.) 1921

47 Rociński and Tychowski. *Polska Gazeta Lekarska*, 1923, pp 4-5

of fluid into the cavum spinale was maintained. For this purpose a needle was inserted into the subarachnoid space either through the membrana atlanto-occipitalis or into the lumbar region. This needle was then connected with an injection apparatus (Fig 7), constructed of a thermos bottle (*A*) closed with a rubber stopper, provided with three glass tubes: the side glass tube (*m*) showed the fluid level inside of the bottle, *n* allowed air to enter and *O* was for outflow, a drop counter (*B*) indicated the rate of the outflow.

Two solutions were used for injections: isotonic 0.9 per cent sodium chloride and Ringer's solution⁴⁸ without glucose. The fluid was injected at or near the body temperature of the animal, the temperature being measured by a thermometer enclosed in rubber tubing close to the injection needle.

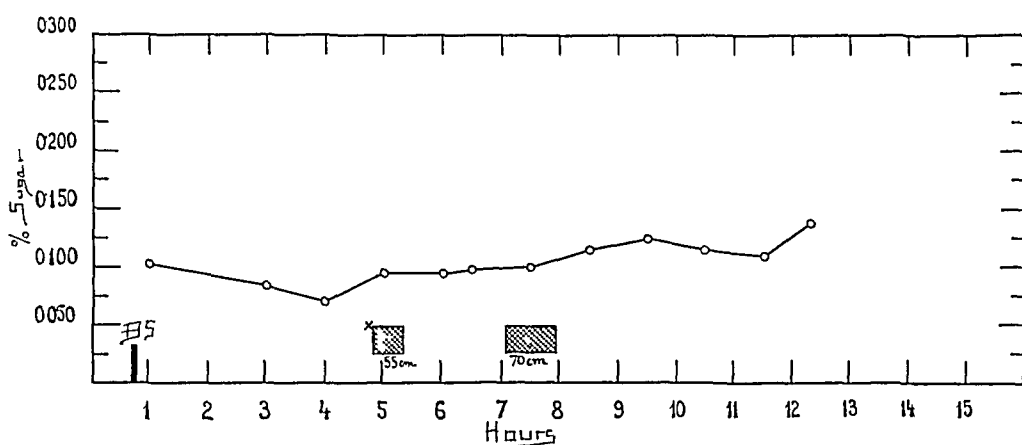


Fig 8—Effect on male cat, weighing 3,400 Gm, of barbital sodium anesthesia, at X puncture of cisterna magna, pressure exerted 55 cm of physiologic sodium chloride solution for thirty-four minutes and 70 cm for fifty-two minutes.

Pressure changes were effected by raising or lowering the entire apparatus. The absolute values, expressed in centimeters of the solution used, were estimated between the needle and the fluid surface level in the tube (*m*).

(a) Continuous Injections of Saline into the Cavum Subarachnoidale from the Cisterna Cerebellomedullaris After Its Puncture. Figures 8 and 9 show experiments performed according to the technic described in the foregoing, the rise of cerebrospinal fluid pressure thus effected also causes an elevation of the sugar level in the blood.

A rise of pressure to 55 cm has no marked effect, values from around 80 to 100 cm are apparently effective. In the experiment of which data are given in Figure 8, 55 cm of pressure for thirty-four minutes was followed by a rise in sugar from 0.071 per cent to 0.090 per cent, and 70 cm pressure during fifty-two minutes changed the

blood sugar from 0.098 to 0.124 per cent, but in the experiment shown in Figure 9, 98 cm of pressure applied for forty minutes produced the change of 0.086-0.128 per cent, and 109 cm during seventy-five minutes, 0.100-0.140 per cent. It should be noticed that the pressure was raised twice in every experiment, each time causing the same positive result.

An analogous series of experiments was performed, using Ringer's fluid. The experiment shown in Figure 10 corresponds to that shown in

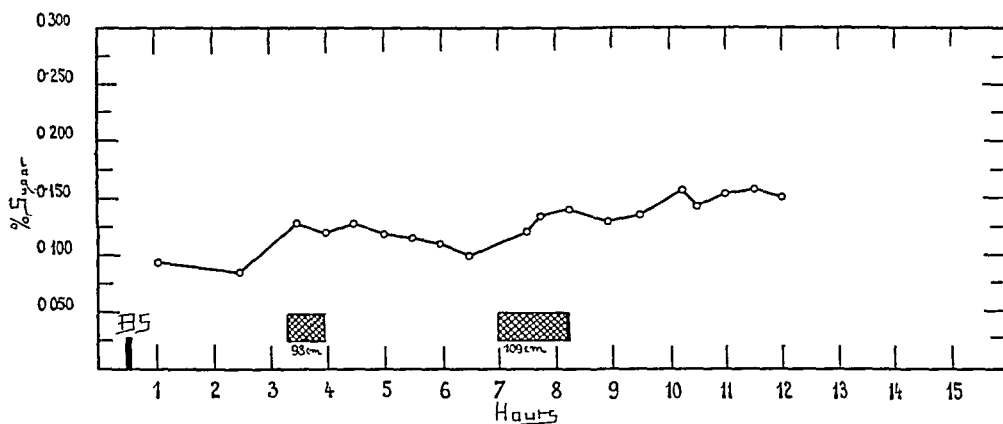


Fig 9—Effect on male cat, weighing 2,700 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, pressure 98 cm for forty minutes and 109 cm for seventy-five minutes

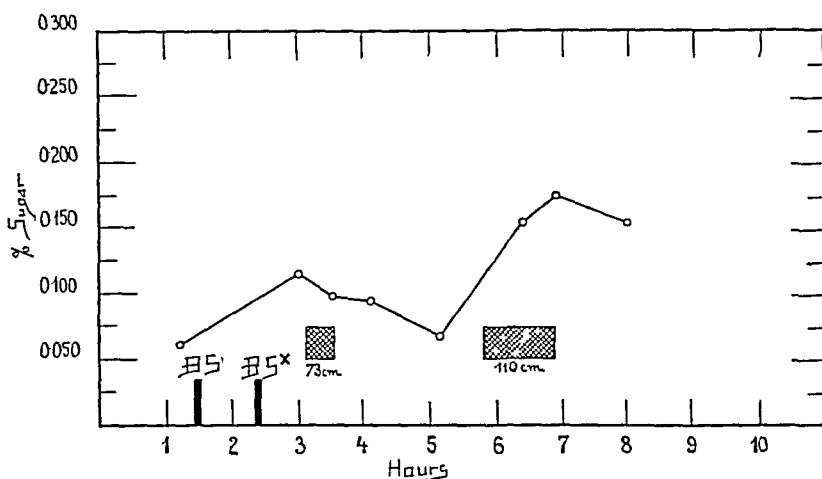


Fig 10—Effect on female cat, weighing 2,600 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, pressure 73 cm for twenty-three minutes and 110 cm for sixty-five minutes

Figure 8 a pressure of 73 cm for twenty-three minutes was without effect, while 110 cm applied for sixty-five minutes caused a change in sugar level from 0.068 to 0.175 per cent

In the experiments of Figures 11 and 12, a pressure of 100 cm of fluid was applied, each time over a period of sixty minutes

The blood sugar level rose in one experiment (Fig 11) from 0.097 to 0.197 per cent and from 0.131 to 0.181 per cent, and in the other (Fig 12) from 0.115, to 0.178 per cent, and from 0.140 to 0.187 cent. In the latter experiment puncture of the cisterna magna preceded the raising of the pressure by two hours and forty-five minutes. High pressures, such as were used in the following case (Fig 13), namely 139 cm for sixty minutes, produced a rise from 0.080 to 0.300 per cent, the second period of pressure, 125 cm for forty minutes was without effect

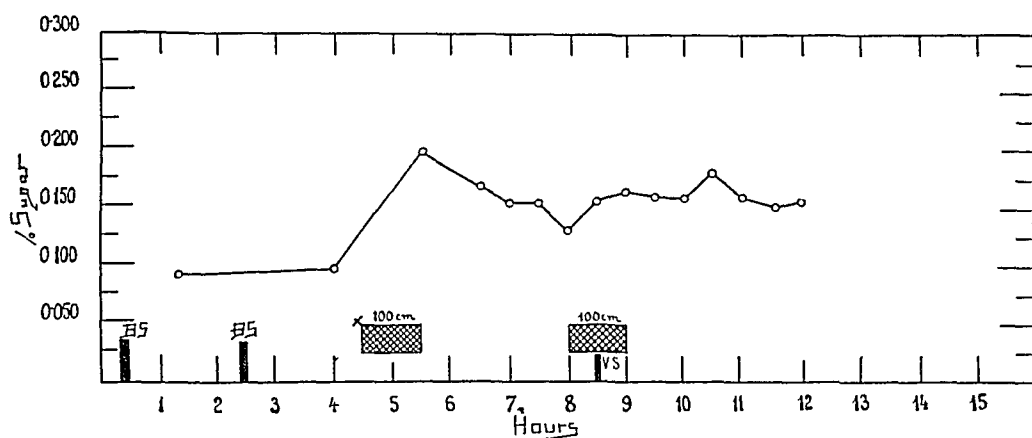


Fig 11—Effect on male cat, weighing 4,080 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, pressure 100 cm for sixty minutes each time

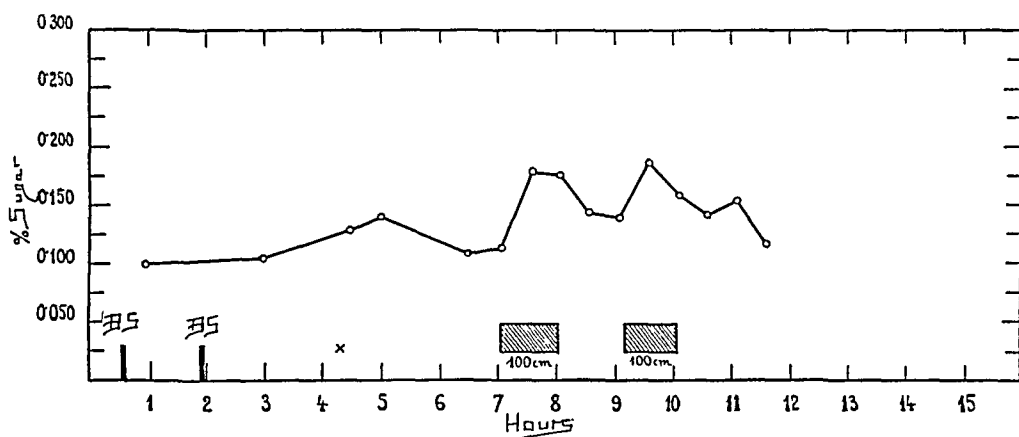


Fig 12—Effect on male cat, weighing 2,900 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, pressure 100 cm of Ringer's solution for sixty and fifty-five minutes

In a few cases the pressure in the subarachnoid space was actually measured by a manometer. Two needles were inserted through the atlanto-occipital ligament into the cerebellomedullar space, one was connected with the pressure apparatus, the other with a manometer. The manometer indicated the pressure in the cisterna and was found to follow closely the applied pressures. The experiment shown in Figure

14 was performed in this manner, fifty minutes of a 50 cm pressure, as shown by the manometer, did not cause any change in blood sugar. In another experiment 90 cm of pressure for sixty minutes (Fig 15) raised the sugar from 0.091 to 0.118 per cent.

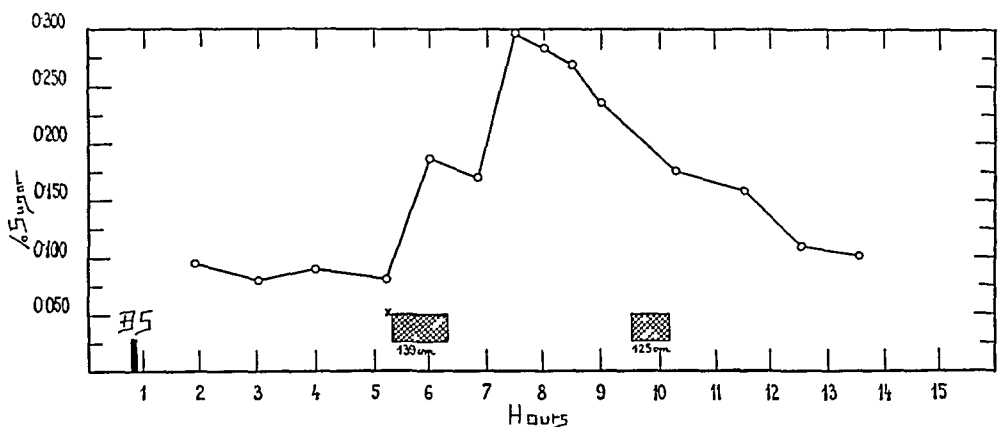


Fig 13—Effect on male cat, weighing 3,200 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, pressure 139 cm of Ringer's solution for sixty minutes and 125 cm for forty minutes.

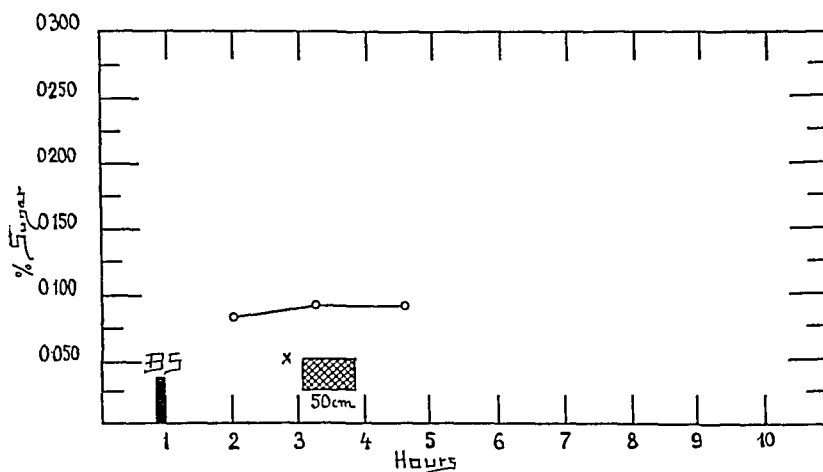


Fig 14—Effect on female cat, weighing 2,800 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, two needles inserted, one connected with a manometer, the other with the pressure apparatus, both filled with Ringer's solution, pressure 50 cm controlled by manometer for fifty minutes, no change in blood sugar.

(b) Continuous Injections into the Cavum Subarachnoidale from the Lumbar Region. To exclude any possible direct stimulation of the medulla oblongata from the operation, the pressure of cerebrospinal fluid was raised in some experiments by lumbar injection. An ordinary lumbar puncture was performed with a fairly large trochar, the outflow of fluid was taken as proof of a successful puncture. Pressures of different values were then applied.

Figure 16 represents such an experiment in which a positive but slight result was obtained in this way Eighty-eight centimeters pressure for thirty minutes produced an insignificant rise from 0.077 to 0.090 per cent, 100 cm for sixty minutes changed the sugar from only 0.080 to 0.098 per cent In another experiment (Fig 17), 78 cm of pressure for sixty minutes raised the sugar from 0.071 to 0.140 per cent, and 80 cm for sixty minutes from 0.089 to 0.155 per cent

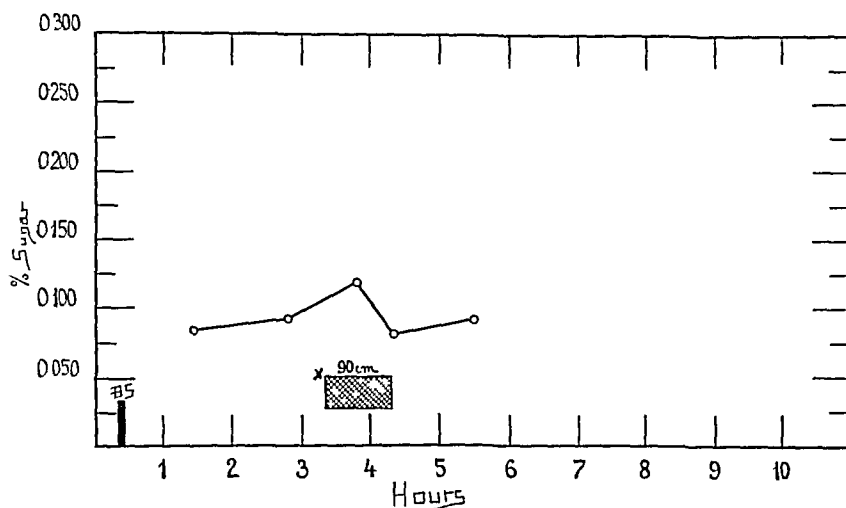


Fig 15—Effect on male cat, weighing 4,000 Gm, of barbitol sodium anesthesia, at X puncture of cisterna magna, two needles inserted, one for pressure apparatus, the other for manometer control, pressure 90 cm for more than sixty minutes

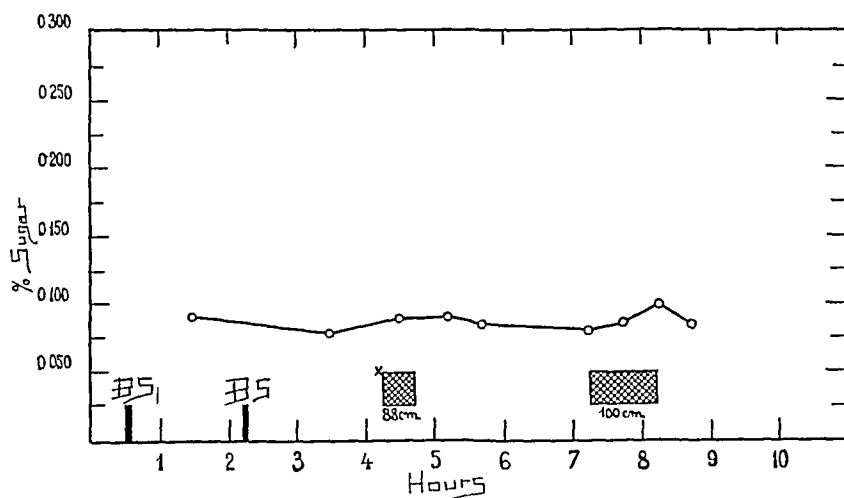


Fig 16—Effect on male cat, weighing 2,700 Gm, of barbitol sodium anesthesia, at X lumbar puncture, pressures 88 cm of Ringer's solution for thirty minutes and 100 cm for sixty minutes

In a single case (Fig 18), both methods of raising pressure were used At first a lumbar injection of physiologic sodium chlorid solution at 100 cm pressure maintained for sixty minutes raised the blood sugar from 0.087 to 0.114 per cent, two and a half hours later, after the

sugar level had dropped to 0.078 per cent, the cisterna magna was punctured and pressure was then twice raised to 110 cm for sixty minutes, this resulted in a change of sugar level from 0.078 to 0.131 per cent the first time, and from 0.103 to 0.119 per cent the second

A number of experiments (seven) were performed on animals under chloroform anesthesia for the reason given at the beginning of the paper

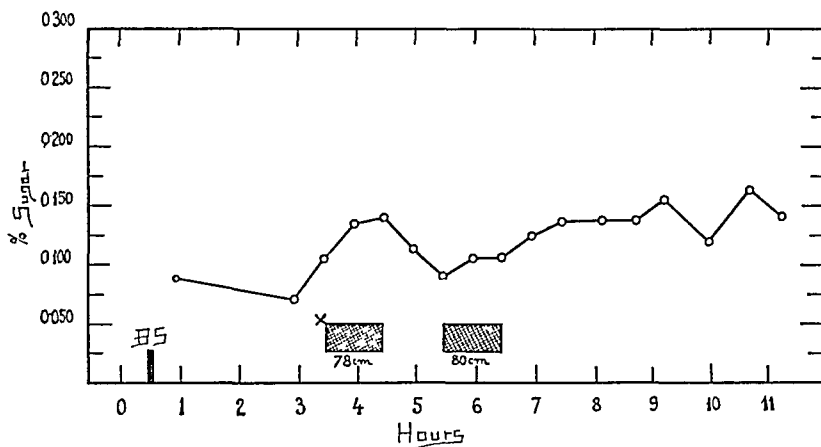


Fig 17—Effect on female cat, weighing 3,175 Gm, of barbitol sodium anesthesia, at X lumbar puncture, pressure 78 cm of Ringer's solution in first period and 80 cm in second, each for sixty minutes

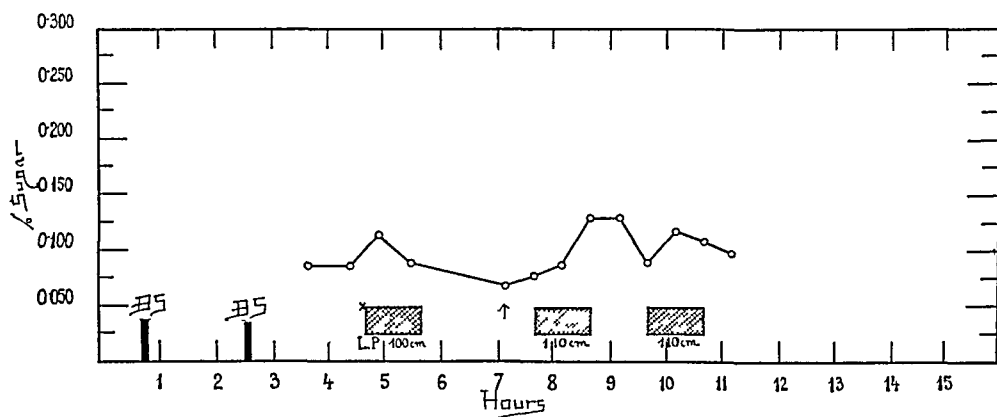


Fig 18—Effect on female cat, weighing 2,300 Gm, of barbitol sodium anesthesia, at X lumbar puncture followed by pressure of 100 cm, at arrow puncture of cisterna magna, followed by pressure of 110 cm applied twice, each time for sixty minutes

Although chloroform itself elevates blood sugar considerably, increased cerebrospinal fluid pressure tended to raise it still more. Figure 19 shows the initial value of blood sugar, 0.193 per cent, one hour after tracheotomy, 93 cm pressure for sixty minutes brought the sugar to 0.234 per cent

A slight fall in sugar percentage followed removal of the pressure, two hours later the sugar rose very high as a result of the prolonged anesthesia. In experiment of Figure 20, the rise of cerebrospinal fluid pressure was caused by an injection of 20 cc of Ringer's solution from a syringe. This sudden change in pressure was followed by an immediate rise of blood sugar from 0.209 to 0.289 per cent.

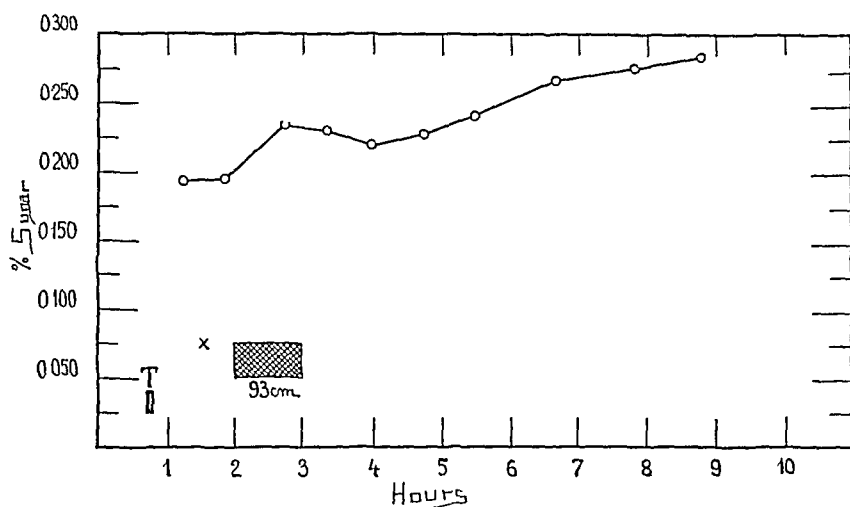


Fig 19—Effect on male cat, weighing 2,800 Gm, of tracheotomy at *T*, under chloroform anesthesia, chloroform continued till end of experiment, at *X* lumbar puncture followed by pressure of 93 cm for sixty minutes

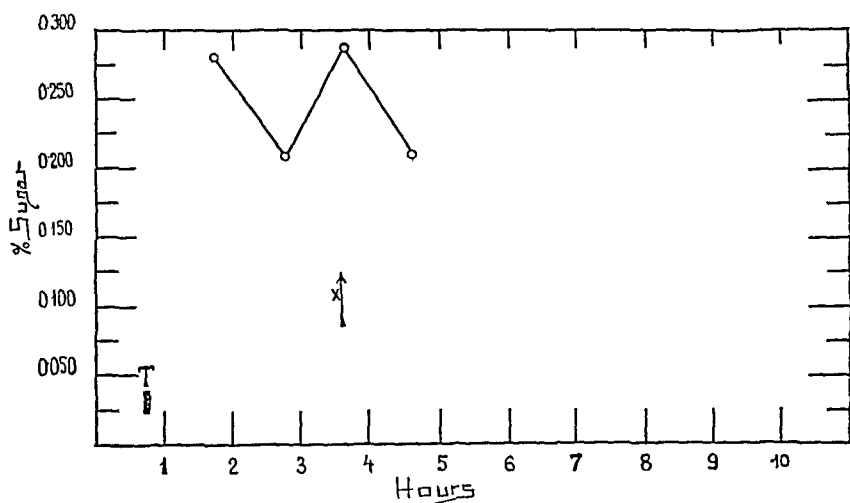


Fig 20—Effect on female cat, weighing 3,200 Gm, of chloroform anesthesia, at *T* tracheotomy, at *X* lumbar puncture, at arrow injection of 20 cc of Ringer's solution from a syringe into subarachnoid space

3 *Effect of Mechanical Pressure on the Medulla Oblongata and of High Cerebrospinal Fluid Tension on Blood Pressure and Respiration*—In about 80 per cent of all experiments a more or less marked change in respiration was observed. A considerable change occurred imme-

diately after injections of blood or paraffin into the cerebellomedullar space, it consisted in a decrease in rate and alteration in the depth of respiratory movements. As a result of continuous fluid injections only after a certain degree of pressure was reached, and then only in the first few minutes after starting the inflow did such changes occur and they were less pronounced. Apparently the pressure affected the respiratory centers of the medulla. The possibility arose that other medullary centers might be altered at the same time, especially the sensitive vasomotor centers and vagus nuclei, both of which are closely connected with the maintenance of blood pressure. Since it is well known that both respiratory disturbances and changes in blood pressure greatly affect blood sugar, it seemed advisable to determine how these altered as a result of the application of our experimental methods. Finkelburg⁴⁹ stated from his experiments on dogs, in which he investigated the transmission of cerebrospinal fluid pressure throughout the craniospinal cavity, that pressure raised in the lumbar region is not exerted to the same degree within the cranium, and that an even more marked difference of levels may be observed when the intracranial pressure is primarily raised. He also noted marked slowing of pulse rate and respiratory movements as the result of pressure from around 80 to 100 mm of mercury, his method of pressure raising was identical with that of continuous saline injection used in the present work, a gradual increase of the pressure followed by its prolonged application did not usually affect the circulatory and respiratory mechanisms.

We performed a series of experiments in which the respiratory movements were recorded by a modification of Cushny's method,⁵⁰ blood pressure was taken with Hurthle's manometer, and the changes in cerebrospinal fluid pressure were also recorded with a sensitive manometer of Hurthle's type connected with the punctured cisterna magna, pressure was applied either by blood injection or by the saline injection apparatus in the usual way.

The injection of 2 cc (Fig 21) of blood into the cisterna magna produced a slight but definite rise in the cerebrospinal pressure which was partly maintained above the previous level, the blood pressure showed a rise of only about 10 per cent, but returned to its previous value within about two minutes, the respiration was irregular, showing long inspiratory pauses, but it also returned to normal within about one and a half minutes. With a larger injection of about 4 cc of blood into the same animal about five minutes after the first, a much greater rise of cerebrospinal pressure occurred (an additional increase of 50 per cent) followed by a gradual drop, though even after many minutes the pressure still

49 Finkelburg *Deutsch Arch f klin Med* **76** 383-412

50 Cushny *J Pharm & Exper Therap* **4** 363, 1913

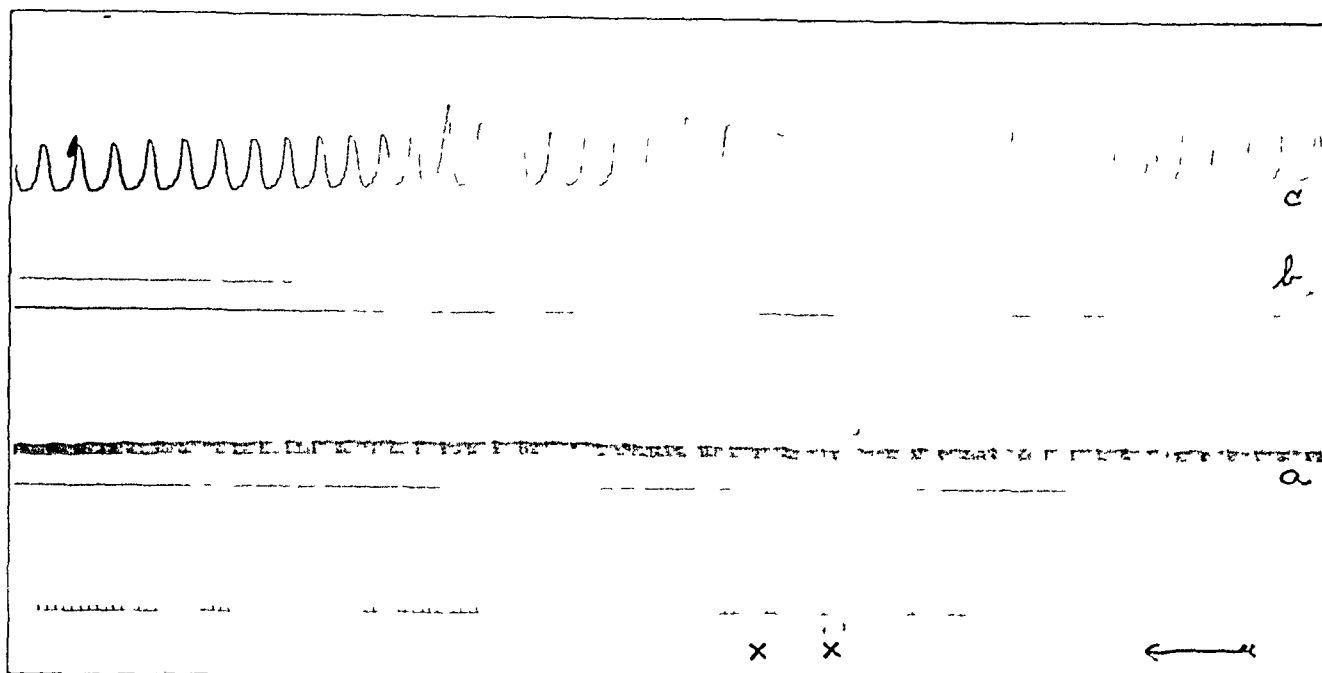


Fig 21—Effect on female cat, weighing 3,000 Gm, of barbital sodium anesthesia, 1-2, injection of 22 cc of blood into cisterna magna, followed by slight rise in cerebrospinal fluid pressure, *a*, blood pressure, *b*, cerebrospinal fluid pressure, *c*, respiration, upstroke—inspiration, after about twenty seconds an insignificant rise in blood pressure (carotid) accompanied by increased pulse pressure, stoppage of respiratory movements immediately after injection was started, record reads from right to left, time marker indicates seconds

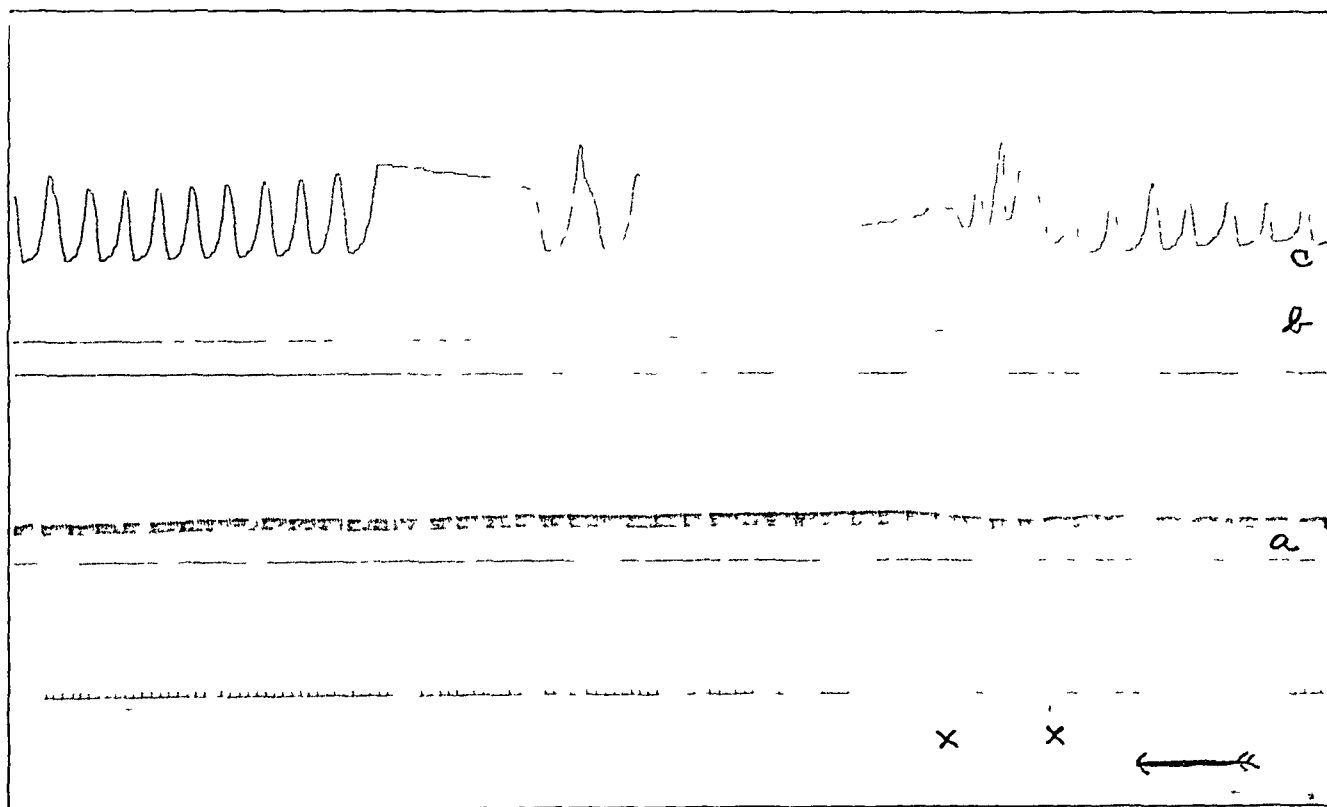


Fig 22—Effect of injection of additional blood into same animal as in Figure 21 (description in text)

remained about 25 per cent above the level at the beginning of the experiment. The blood pressure changes were still slight (about 20 per cent) and the previous level was regained within three minutes, the respiratory changes were much more marked, long inspiratory spasms occurring (Fig 22 indicates type of result obtained)

When saline is injected into the cisterna magna continuously and slowly so that the pressure rises much more gradually the effect on the respiration is much less, there being a marked slowing of the respiratory movements. Figure 23 indicates the blood pressure and respiratory changes seen as the result of raising the pressure in the cisterna magna to 100 cm of saline pressure. Similar results were obtained to those reported by Finkelnburg,⁴⁹ Naunyn and Schreiber,⁵¹ but were obtained with much lower pressures.

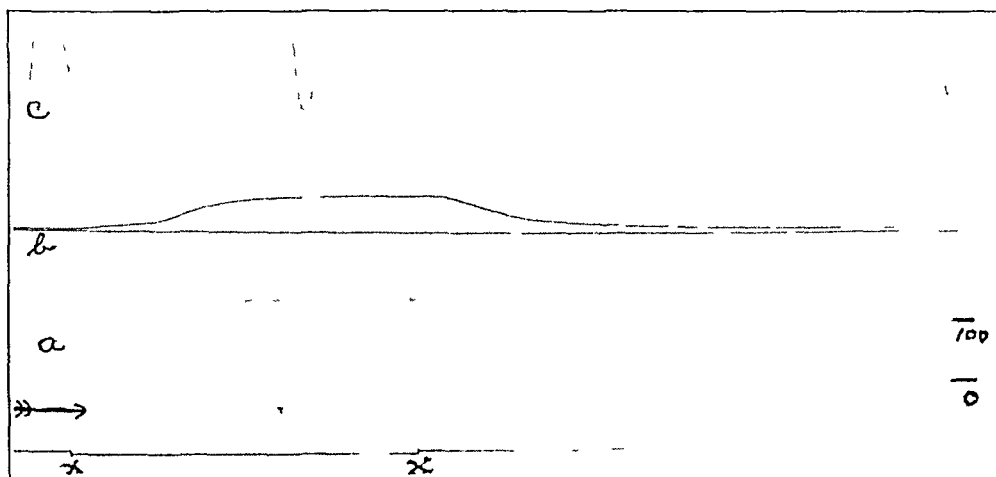


Fig 23—Effect on female cat, weighing 2,800 Gm, of barbital sodium anesthesia, blood pressure taken from the carotid, respiration recorded by the spirometer, two needles inserted in cisterna magna, one connected with Hurtle's manometer, the other with the pressure apparatus, *x-x*, raising of cerebrospinal fluid pressure to 100 cm of Ringer's solution

COMMENT

In these experiments every effort was made to eliminate factors that might complicate results. Temperature, active digestion, the so-called "Fesselungshyperglykaemie" and anesthesia, any or all may have come into play, their possible influence is to be considered.

Temperature was controlled by frequent observations of a rectal thermometer. The slight fall attending the early hours of the anesthesia was prevented by the use of a heating arrangement and body temperature did not vary over a few tenths of a degree Centigrade. Even greater variations than this occur physiologically and apparently do not affect

blood sugar The intake of carbohydrates from the alimentary canal was nil, the animals being starved for at least sixteen hours before the first blood sample was taken "Fesselungshyperglykaemie" was avoided by the use of anesthetics, the animals lay unconfined on the operating table

The influence of anesthetics has already been described In seven experiments performed under chloroform there was a high sugar level, which after several hours of a fairly steady level rose even higher This may well correspond to the exhaustion of chromophil material in prolonged narcosis observed by Schur and Wiesel⁵² and confirmed by Borberg McGuigan and Ross⁵³ noted an increase of blood sugar even in moribund animals immediately before death, observations which may explain cases in the present work in which the sugar went up at the end of the experiment apparently without reason The total period of observation of the chloroform narcoses was considerably shorter than the others, never more than five hours, because of secondary changes from the prolonged anesthesia, i e, exhaustion of available glycogen, toxic effect of chloroform on heart muscle and liver tissue, and dehydration of the animal, consequent on breathing through the tracheotomical cannula Under these limitations the most favorable time for actual experimentation was the first two or three hours after the beginning of anesthesia, when these factors were not yet potent enough to obscure results, but late enough to avoid the effect of tracheotomy The experiments under chloroform showed in general similar results to those under other anesthetics Even such high sugar levels as from 0.15 to 0.21 per cent were elevated by the use of pressure on the medulla oblongata

In the first series of experiments, in which the subarachnoid space near the medulla oblongata was entered, the possibility of injury to the bulb or cervical cord, or even of a regular piqûre, all of which might result in hyperglycemia, was a pertinent danger To avoid these the needles were introduced very slowly and directed upward to one side After the experiment a necropsy was always performed and the spinal cord and bulb macroscopically examined for injury The second series of experiments excluded this danger because pressure was applied from the lumbar region, results were just as positive

To maintain a constant hydrostatic pressure continuous injections were made, the fluid, physiologic sodium chlorid solution or Ringer's solution was allowed to flow in for from twenty-three to seventy-five minutes Besides pressure changes two other possible effects of such

52 Schur and Wiesel *Wien klin Wchnschr*, 1908

53 McGuigan and Ross *J Biol Chem* **22** 418, 1915

prolonged injections are to be considered, first, the dilution of the cerebrospinal fluid, with its resultant chemical effect on the central nervous system, second, the resorption of a considerable amount of the injected fluid into the blood and lymph, with a consequent change in blood volume. As to the first, neither fluid showed any influence on blood sugar, even when used over long periods, this is shown when the flow of fluid into the subarachnoid space was continued for hours under low pressure without change of blood sugar. The possible chemical effect on the nervous system of the potassium and calcium salts in the fluids used is to be especially considered, since Hooker⁵⁴ and Mathison⁵⁵ demonstrated their stimulative powers on medullary and spinal centers. However, not only because of the low concentration but also because of the antagonistic action of calcium to potassium ions, both of which are present in Ringer's solution, any effect is absent, as proved by Heinekamp⁵⁶. Even should toxic effects appear, the changes in the tissues must remain and recovery would be impossible within the time of the experiment. Actually, however, repeated raising and lowering of the pressure resulted in increases and decreases, respectively, of the sugar content of the blood. This marked sequence of the blood sugar variations to pressure changes suggests strongly that the mechanical factor alone is responsible for the final effect.

Probably the second possibility, a change in blood volume through resorption, actually does take place, but the effect on blood sugar must be a lowering of its percentage, and any slight degree of hydremia which may have developed from the prolonged injection would tend rather to obscure than to accentuate the simple pressure effects.

The time between sugar estimations varied from fifteen to sixty minutes. Even within such intervals oscillations in blood sugar content may occur. However, it seems that the sugar curve was followed closely enough for the purposes of this work. The stimuli applied were, in the case of continuous injections, of considerable duration and their effects, if any, probably last longer than fifteen minutes, our shortest interval. Moreover, in the course of the work it was found that the changes in blood sugar from such rather weak though prolonged stimuli occur slowly, so that the usual interval of thirty minutes was close enough to follow them accurately.

There remain about 10 per cent of the experiments, in which results were negative. The larger number of these followed stimulation by hydrostatic pressure, only in a few cases was the injection of blood ineffective. As to the first series, it seems that a certain degree of

54 Hooker *Am J Physiol* **38** 200-208, 1915

55 Mathison *J Physiol* **13** 471-494, 1911

56 Heinekamp, W J R *J Pharm & Exper Therap* **19** 239-245 (April) 1922

pressure can be applied with practically no effect on sugar. If values around 100 cm are reached, changes are marked. It was also noted that the same degree of pressure exerted through a large trocar produced a more marked effect than pressure applied through a small bored needle. Thus, rate of the initial change of pressure seems to be a factor of great importance. Negative results in cases of blood injections may also be easily explained, and in some experiments (Figs 5 and 6) were expected, for the blood was purposely injected in a small amount, 0.5 cc, and the injection performed very slowly. Thus conditions were not favorable to the development of pressure, the small amount of fluid introduced under low pressure over a comparatively long time was easily taken care of by resorption of a corresponding amount of cerebrospinal fluid, and the insignificant change in pressure during the injection was apparently far below the stimulation threshold.

Moreover, on a starved animal even Bernard's piqure is ineffective, because of lack of available glycogen. The cats in the present work were without food—for other reasons—for at least sixteen hours before being used, and their previous food was not especially rich in carbohydrates. The resultant low glycogen should then be considered as probably an important factor in cases of negative or only weakly positive results.

Finally, the depressive effect of the anesthetics on the central nervous system must be taken into account. Although the doses used were not excessive and corneal reflexes were usually present, it is to be expected that under physiologic conditions the same stimulation would produce a more marked hyperglycemia.

Explanation of the positive results obtained in this work is closely related to the theories concerning Bernard's piqure. Though used in experimental work for more than half a century, the piqure was performed without accuracy or definite location, experimenters limited themselves to macroscopic examination of the involved part of the medulla oblongata, and only recently Brugsch, Dresel and Lewy⁵⁷ first used systematic histologic controls, following both positive and negative piqures. Their work led them to state that the essential agent in the production of piqure-hyperglycemia is a lesion of the so-called "sympathetic" nucleus nervi vagi, which contains not only sympathetic but also parasympathetic cells. They were able to state further that minute hemorrhage near this center could, without actually destroying the cells, produce a stage of "irritation" characterized by microscopic changes, such as are sometimes produced by partially successful piqure, and that this also was followed by hyperglycemia. Moreover, they found

⁵⁷ Brugsch, T., Dresel, and Lewy. *Ztschr f exper Path u Therap* **21** 358-379, 1920, *Ztschr f d ges exper Med* **25** 262-270, 1921.

that lesions of different parts of this nucleus produced contrary changes in blood sugar, they consider that injury of the caudal part involved the sympathetic cells concerned in activation of the suprarenals, and so represented the common *piqûre* lesion, the rostral segment, which includes the vagus parasympathetic central elements, they considered to be related to the internal secretion of the pancreas and thought that its stimulation leads to increased polymerization of glucose into glycogen.

Closely related to this sympathetic nucleus *nervi vagi* is a group of ganglionic cells situated in the hypothalamus, which was discovered by retrograde degeneration and described by Molhant⁵⁸. This nucleus *paraventricularis*, located close to the third ventricle, is considered by many to be a center superposed in a functional sense to the nucleus *sympatheticus nervi vagi*, the relation is suggested by certain anatomic changes occurring in both nuclei in cases of paralysis agitans, observed by Lewy. The relation of the nucleus *paraventricularis* to carbohydrate mobilization is not yet clear, but the anatomic findings of Lewy seem to indicate that the two centers collaborate to increase sympathetic tonus, which is considered by some essential to the development of hyperglycemia.

The mechanical pressure applied to the medulla must affect not only the sympathetic and the paraventricular nuclei but also other medullary centers. The changes in respiration that resulted were at first only observed and noted, but in later experiments they were also recorded. An analysis of the curves obtained shows a decrease in both rate and depth, of respiratory movements. The consequent deficient lung ventilation followed by lowered hemoglobin saturation may induce anoxemia, which is known to create a powerful stimulus toward the development of hyperglycemia. Such changes should occur provided the pressure does not stimulate other and more powerful antagonistic centers.

The nucleus *motorius nervi vagi* is largely concerned with the innervation of not only the abdominal but also the thoracic viscera, most important of these are the heart and the lungs. Blood pressure tracings obtained from the carotid did not indicate any marked cardiac changes, far more complicated are the vagal effects on the lungs. Fibers innervating the bronchial system can greatly influence the individual lumina and these may so alter the air exchange as to bring on anoxemia. Vagus stimulation may also alter the patency of the pulmonary blood vessels through their rich vasomotor supply, a fact demonstrated by Krogh⁵⁹ and by Carlson and Luckhardt,⁶⁰ and thus in still another way may

58 Molhant. *Nevraxe*, Louvain, 1910, pp 137-244

59 Krogh. *Zentralbl f Physiol* 20 802, 1907

60 Carlson, A. J., and Luckhardt, A. B. *Am J Physiol* 56 7-2112 (May) 1921

regulate the air exchange. All these factors might be combined at once from medullary stimulation but the final effect would be asphyxia.

Macleod⁶¹ and Griffith⁴⁴ demonstrated by experimentation that stimulation of the central end of the vagus produced a rise in blood sugar, Rossi⁶² after similar stimulation of the vagus found a diminution of the glycogen content of the liver. These experiments show that the afferent fibers of the vagus are concerned in the metabolism of carbohydrates.

In our experiments whenever blood pressure was recorded it preserved an almost constant level. The slight rise that did occur was preceded by changes in respiration and did not take place immediately after medullary compression but only after a certain latent period. The fact that this rise was slow to appear indicated that it was a response of the vasomotor centers either directly due to the pressure or secondary to the respiratory changes. Winkin⁶³ showed that the cutting off of the arterial circulation to the head produced a marked vasoconstriction, she further showed that both splanchnic nerves together with their secretory fibers to the suprarenals are pathways for impulses originating in the vasomotor centers and passing down to the peripheral organs. The increased output of epinephrin which is said to follow central stimulation and to maintain the primary vasoconstriction may be responsible for the sugar mobilization. Cannon and Rapport⁶⁴ state the existence of a reflex center for epinephrin secretion which they believe to be located on the floor of the fourth ventricle and to be the recipient of both excitatory and inhibitory impulses. In either case, be it alteration of vasomotor centers or stimulation of Cannon's epinephrin center, medullary pressure may result in an increased discharge of epinephrin followed by an increased sympathetic tonus and subsequent hyperglycemia, this fits in well with the theory of hyperglycemia which has been widely accepted since Blum's discovery of the glycosuric effect of epinephrin. The action of epinephrin was thought by Masing⁶⁵ to be manifested by a lowered gas exchange in the isolated liver, according to Neubauer⁶⁶ it produces an anoxybiotic state in the liver, Starkenstein⁶⁷ believes that stimulation of the sympathetic results in a change of the physical constitution of the cells, which represents a uniting link between ferment action and sympathetic nerve endings, consisting in an alteration of osmotic pressure and surface tension. Gottschalk and

61 Macleod. *Am J Physiol* **19** 388, 1907

62 Rossi. *Arch di fisiol* **14** 273-277, 1916

63 Winkin. *Proc Soc Exper Biol & Med* **18**, 1921

64 Cannon, W. B., and Rapport, D. *Am J Physiol* **58** 308 (Dec.) 1921

65 Masing. *Arch f exper Path u Pharmacol* **69** 431-457, 1912

66 Neubauer. *Biochem Ztschr* **43** 335-345, 1912

67 Starkenstein. *Ztschr f exper Path u Therap* **10** 78-119, 1911-1912

Pohle⁶⁸ make the change of hydrogen ion concentration in the blood of the portal vein and in liver tissue fluid responsible for the glycosuric action of epinephrin

The survival of the hyperglycemia in some of our experiments beyond the application of medullary pressure may correspond to the observations of Billigheimer,⁶⁹ and those also of Hetényi and Lax,⁷⁰ in which the epinephrin hyperglycemia far outlasted the changes in blood pressure and pulse rate

A quite different view of the origin of hyperglycemia from intracranial changes is advanced among others chiefly by Cushing⁷¹ and recently by Brugsch, Dresel and Lewy⁷² By experimentation he seems to have demonstrated some influence of the posterior lobe of the hypophysis cerebri on carbohydrate metabolism, the product of its secretion first enters into solution in the cerebrospinal fluid, then probably by way of the dural sinuses passes into the blood stream He considers that compression of the aquaeductus sylvii by tumors or lesions of the posterior lobe by trauma may alter the production or transportation of this secretion and in consequence may produce a hyperglycemia

Another attempt to introduce the endocrine system as a factor in the regulation of carbohydrate metabolism was made by Eppinger, Rudinger and Falta⁷³ They proposed an interrelationship between the secretions of the suprarenals, the hypophysis and the thyroid, and supposed that the level of blood sugar was determined by changes in the balance of these glands

Our own results do not give any evidence as to the mode of origin of the hyperglycemia, except that it seems improbable that it results simply from asphyxia secondary to the respiratory changes, since the accompanying blood pressure alterations give no indication of any severe asphyxia

SUMMARY

This work was calculated to reproduce pathologic conditions taking place in cases of disease of the nervous system associated with hyperglycemia, in which either local mechanical compression of the medulla oblongata or general rise of the cerebrospinal fluid tension followed by compression of the whole central nervous system is essential

68 Gottschalk, Alfred, and Pohle, E Arch f exper Path u Pharmacol 95 64-74, 1922

69 Billigheimer, E Deutsch Arch f klin Med 136 1-32 (April) 1921

70 Hetényi and Lax Biochem Ztschr 125, 1921

71 Goetsch, Cushing, and Jacobson Bull Johns Hopkins Hosp 22 165-190, 1911, *ibid* 24 40, 1913

72 Brugsch, T, Dresel, and Lewy Verhandl d deutsch Gesellsch f inn Med 34 347, 1922

73 Eppinger, Rudinger, and Falta Ztschr f klin Med 66 1-52, 1908, *ibid* 67 380-398, 1908

The analogy consisted in applying local mechanical pressure on the medulla oblongata and general hydrostatic pressure on the whole central nervous system

Both procedures, applied experimentally on cats, were followed by a rise in the sugar content of the blood

Hyperglycemia, thus artificially produced in animals, represents in pertinent clinical cases a chronic type of piquê, which may have several factors concerned in its causation

Book Reviews

MEDICAL AND SURGICAL REPORT OF THE ROOSEVELT HOSPITAL, NEW YORK Second series, 1925 Pp 378, 47 illustrations Cloth Price, \$5 net New York Paul B Hoeber, 1925

This is the second medical and surgical report of the Roosevelt Hospital, the first was published in 1915, and this number was to have been published in 1920 but was delayed because of the war. It contains articles on various topics by members of the staff. Some of the articles were written expressly for this report but many articles that have been published elsewhere are included.

The articles in this volume are on a wide variety of subjects and over half are contributed by a relatively small group of workers. Most of the articles are in the nature of case reports, statistical compilations or general discussions on some topic of universal interest. There is little evidence of medical research work contained in them. The illustrations are excellent and well reproduced.

This book should be of interest to a rather special group of medical men but would be of little if any value to the student and the general practitioner.

THE STOMACH AND UPPER ALIMENTARY CANAL IN HEALTH AND DISEASE By T Izod BENNETT, Assistant Physician to the Middlesex Hospital and Physician to the Royal National Orthopaedic Hospital Price, \$6 New York William Wood & Co

The first five chapters of this book contain much practical information relative to conditions of the mouth, tongue, teeth, salivary glands, tonsils and pharynx. In the following chapter the various disorders of the esophagus are discussed briefly and their treatment is outlined. Eight chapters are devoted to the stomach. Its physiology is described and the pathology, symptoms and treatment of its organic and functional diseases are carefully considered. In the last three chapters of the book the author discusses aerophagy, under-nutrition, and the rôle of hepatic and pancreatic disease in digestive disorders.

In all the book may be said to be well worth reading. It is designed for students and practitioners of medicine. It is extremely practical and concise, and is not overloaded with theory and detail. The indications for the surgical treatment of peptic ulcer are definitely listed as are those for the medical treatment in which the author enthusiastically recommends the method introduced by the late B W Sippy. Many of the old erroneous notions of gastrointestinal disease are carefully dispelled. The book marks a definite advance in the literature of the gastro-intestinal tract and one feels regret that the author has not continued his discussion to include the lower part of the alimentary canal.

BLOOD PRESSURE IN WOMEN AS INFLUENCED BY THE SEXUAL ORGANS¹

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AND

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Several years ago when one of us (W C A) analyzed the records of blood pressure in 15,000 University of California freshmen and 1,000 office patients, he was much impressed by the fact that the data from the women were so different from those of the men. Thus, when we turn to the report of that work,¹ we note, first, that the mean pressure for the women was 10 mm less than that for the men until the late forties, when the women's pressures averaged higher than those of the men. More striking was the fact that whereas 20.7 per cent of the young men had pressures over 140 mm, only 2.7 per cent of the women were similarly affected.

In all fairness, it should be noted at this point that Diehl and Sutherland² have just shown that if the men students with the high readings are allowed to rest a while, or if they are examined repeatedly so that they can lose some of their nervousness, 49 per cent ultimately show lower pressures, 25 per cent will vary up and down, and 15 per cent will maintain the high level. Eleven per cent were excluded from consideration because their hypertension was thought to be of the secondary type.

At first sight, this might seem to wipe out a good deal of the difference between the pressures of men and women, but we must remember, first, that it is not good statistical practice to take just the data that fail to agree with our previous conceptions and to work with them until they do agree, if we are going to modify some of our data we should modify all of them, second, much of our own unpublished work on these boys with transient and intermittent hypertension makes us feel that their

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¹ Alvarez, W C. Blood Pressure in University Freshmen and Office Patients, *Arch Int Med* **26** 381 (Sept) 1920, Blood Pressures in Fifteen Thousand University Freshmen, *ibid* **32** 17 (July 15) 1923.

² Diehl, H S, and Sutherland, K H. Systolic Blood Pressures in Young Men, *Arch Int Med* **36** 151 (Aug 15) 1925.

peculiarity does mean something for their futures, and that it cannot be lightly reasoned away, and, third, even if we do discard these cases, there still remains a big difference between the incidence of hypertension in men and in women. Diehl and Sutherland found 5.6 per cent of their men students with permanent or intermittent hypertension and 1.2 per cent more with "secondary hypertension"—all over 140. This gives 6.8 per cent, which compares well with Alvarez' figure of 7.6 ± 0.2 per cent for men with pressures of 150 mm and over—men that were almost certainly abnormal. Even if we follow Diehl and Sutherland and exclude 5.1 per cent of Alvarez' group of men with pressures over 140 mm, we still have 10.2 per cent to compare with the 2.7 ± 0.1 per cent among the women.

This difference between men and women can be brought out even more clearly perhaps by pointing to the fact that at the University of California there were 3.6 times as many men as women with pressures over 130, 7.5 as many with pressures over 140, 1.4 times as many with pressures over 150, and 30 times as many with pressures over 160 mm.

As we might have expected, this big difference between the pressures of men and women appears about the time of puberty.³ Before that the pressures in the two sexes are about the same.⁴ It is interesting also that in both the young men and the young women the pressures are highest about 17. After that they drop a little until about the age of 28 in the men, and 24 in the women. The rise that then takes place in the mean pressure is more rapid in the women than in the men, so that after 45 or 50 the women average higher than the men.

Another sexual difference comes out clearly when we compare the distribution curves based on the data from men and women. Then we see that the curves for the women are high and narrow while those for the men are low and wide. This difference appears about the age of 17. In the language of the statistician, the standard deviation and the coefficient of variation are lower for the women up to the age of 35. After that, these indexes are higher for the women than for the men.

HEREDITY AND HYPERTENSION

Now, something that appears so strikingly in college freshmen of 17 and 18 can hardly be ascribed to the wear and tear incident to old age or to the strenuous life, and something that varies so markedly in the two sexes is not likely to be due to such things as focal infections or

3 Burlage, S. R. The Blood Pressures and Heart Rate in Girls During Adolescence, *Am J Physiol* **64** 252 (April) 1923.

4 Judson, C. F., and Nicholson, P. Blood Pressure in Normal Children, *Am J Dis Child* **8** 257 (Sept.) 1914. Faber, H. K., and James, C. A. The Range and Distribution of Blood Pressures in Normal Children, *Am J Dis Child* **22** 7 (July) 1921.

intestinal autointoxication, which we would expect to find pretty evenly distributed between the two groups. If constipation has anything to do with it, we should expect to find somewhat more hypertension in the girls than in the boys.

It would seem more probable, then, that we must be dealing with some bodily peculiarity which is distinctly modified by sex, especially at the crises of puberty and the menopause. But where does the peculiarity come from? Almost certainly from our ancestors. For years one of us (W C A) has been impressed by the high incidence of hypertension which he has observed in the relatives of those complaining of this disease, and a search through the literature shows that several writers have commented on the same thing. Family records such as that published by Rosenbloom⁵ are striking, but the statistical studies of O'Hare, Walker and Vickers,⁶ and of Weitz⁷ are still more convincing. O'Hare and his associates studied 300 persons with hypertension and 436 without hypertension or other cardiovascular-renal disease. In the first group there was a history in one or more relatives of apoplexy, heart disease, nephritis, arteriosclerosis or diabetes in 68 per cent, while in the second or control group such a history could be obtained in only 37.6 per cent. Weitz found that half of the sibs of some eighty-two patients with hypertension had hypertension or had already died of it. Three fourths of their parents had died of strokes, heart disease or other conditions suggesting the presence of the hypertensive diathesis. In his control group of 267 subjects—unfortunately not so well studied—he found 30 per cent of parents with suggestive histories. Although this work leaves much to be desired from the standpoint of the geneticist and the biometrician, it is suggestive and points the way to some more extensive and more careful work by men who have had special training in this field.

THE SEXUAL FACTOR

If, then, we follow the lead of this evidence and assume that the main factor in producing hypertension is a hereditary predisposition, we must next explain the fact that the men develop it early and the women develop it late. If the women inherit the tendency equally with the men—and we have no reason to assume the presence of any sex linkage—what holds it latent in the earlier years? Certainly it would seem to be the internal secretions that have so much to do with sexual

⁵ Rosenbloom, J. Familial Hypertension, with Report of a Case, *J. Lab. & Clin. Med.* 8:681 (July) 1923.

⁶ O'Hare, J. P., Walker, W. G., and Vickers, M. C. Heredity and Hypertension, *J. A. M. A.* 83:27 (July 5) 1924.

⁷ Weitz, W. Zur Aetiologie der genuinen oder vascularen Hypertension, *Ztschr. f. klin. Med.* 96:151 (Jan.) 1923.

development As one of us¹ has pointed out, there are many things about the plumage changes that hens show after ovariectomy that are suggestive in this connection As is well known, these hens come to look like cocks, and it may be that in women, hypertension emerges at the menopause much as hair emerges on the face—and for the same reason

This theory would receive great support if it could be shown that a considerable proportion of young women who are born with poor ovaries, or who early in life lose a large part of the functioning tissue through disease or by operation, promptly develop hypertension Naturally, we would not expect all such women to develop it because many of them would not be carrying the tendency They would belong to that group of men and women who go on into their seventies with pressures under 130 mm of mercury

MATERIAL USED

The present study is based on the analysis of some 1,230 records taken from the office files of one of us (W C A) The great advantage of these records is that they were made almost entirely by one man, who, for a good part of the time, was interested in the solution of the problem before us The patients for the most part came complaining of gastro-intestinal troubles or, at least, what they thought were gastro-intestinal troubles, so that they have not been selected for either hypertension or ovarian disease In all but a few cases, a pelvic examination was made, and in most of the cases in which abnormalities were found in that region, the findings were checked by an expert gynecologist Unfortunately, in spite of this carefulness, there were a good many of the records which were not complete on all points and which could be used only for certain phases of the inquiry

The women on whose findings this study is based were almost entirely from the middle and upper classes All were white The blood pressures were taken with a good mercury instrument, and the auscultatory readings were used The diastolic pressure was taken at the end of the third phase The patients were all reclining When borderline pressures were found, several readings were taken during the course of the examination—usually spread over several days—and either the mean or the modal pressure was taken for the purposes of this study

The histories were abstracted on cards on which note was made of the name of the patient, her civil status, age, number of children, menstrual history, history of pelvic disease and operations, pelvic findings, weight and build, condition of breasts, distribution of hair, sexual anesthesia, thyroid disease and blood pressure

CRITERIA OF ABNORMALITY

These cards were then sorted by one of us (W C A) into three piles, designated sexually normal, sexually abnormal one plus, and sexually abnormal double plus. While this classification was being made the blood pressure record was covered up so that a mental bias might not enter into the decision in regard to the many borderline cases. These decisions were particularly difficult when the data were not as complete on all points as they should have been. As we shall see later, a few of the criteria on which this classification was based were probably not significant or valid.

A typical subject classed as sexually deficient would have to have one or more of the following points in her history or findings: irregular, painful, scanty, or very profuse menstruation, late onset of menstruation or early menopause, early ovariectomy or hysterectomy for ovarian disease or for fibroids, infantile uterus, undeveloped breasts, fibroids, pathologic overweight, masculine distribution of body and facial hair, mannishness, sexual anesthesia, thyroid disease.

Naturally, little importance could be attached to a history of nulliparity as it is so often voluntary or due to defects in the husband. When, however, a woman had had a large family this fact was used to discount somewhat any slight signs which she might have of hypogonadism. In a number of cases we were helped by having a record of the findings at operation.

Women whose pelvic disease seemed to be due to the effects of gonorrhea or of peritonitis following criminal abortions were generally classed with the normal unless there were some signs or symptoms pointing to preexistent ovarian dysfunction. Naturally, the classification of many of these cases was difficult, and certain facts which will be brought out toward the close of the paper suggest that for our normal standards we should have excluded all those with any type of pelvic trouble which could possibly have damaged the ovaries or their circulation.

THE CORRECTION OF THE DATA FOR DIFFERENCES IN AGE DISTRIBUTION

We had next to divide our data into groups according to the ages of the subjects. In order that these groups might not be too small for statistical purposes, we grouped together ages 16-29, 30-39, 40-49, and 50 and over. It would be obviously unfair to compare the blood pressures of any two groups of women unless we could correct in some way for differences in the age distributions. The need for such a correction might be avoided if we could always have equal numbers of persons of the same ages in the two groups studied, but that is gen-

erally difficult of attainment. We would rather find some way of using all our material and then correcting each mean by a factor based on differences in the age distributions of the particular group and a "standard" group. In order to secure this standard group we took the readings from 573 women who, according to the criteria listed in the preceding section, were normal sexually. These were divided into the

TABLE 1—*Sexually Normal Group* *

Blood Pressure	Age Groups								All Ages Together	
	16-29		30-39		40-49		50+			
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent
90 to 99	1	0.7	4	2.5	2	1.8			7	1.2
100 to 109	13	8.7	15	9.5	4	3.6	3	2.0	35	6.1
110 to 119	58	38.7	36	23.0	16	14.5	12	7.7	122	21.3
120 to 129	50	33.3	48	30.5	21	19.1	10	6.4	129	22.6
130 to 139	18	12.0	33	21.0	26	23.6	28	18.0	105	18.3
140 to 149	7	4.7	11	7.0	21	19.1	33	21.2	72	12.6
150 to 159	1	0.7	5	3.2	11	10.0	18	11.5	35	6.1
160 to 169			1	0.6	4	3.6	16	10.2	21	3.7
170 to 179	1	0.7	2	1.2	2	1.8	10	6.4	15	2.6
180 to 189					1	0.9	6	3.8	7	1.2
190 to 199			1	0.6	1	0.9	5	3.2	7	1.2
200 to 209			1	0.6			4	2.6	5	0.9
210 to 219					1	0.9	1	1.6	2	0.3
220 to 229	1	0.7					3	2.0	4	0.7
230 to 239							4	2.5	4	0.7
240 to 249							3	2.0	3	0.5
Total	150	26.0	157	27.4	110	19.2	156	27.3	573	
Mean	122.1		125.8		135.3		154.4		134.5	
S. D.	13.9		16.0		19.3		30.7		25.0	
P. E. of mean	0.8		0.8		1.2		1.7		0.7	

Correction for weight $134.5 \times 0.995 = 133.8$

Age and Weight Distribution

Age Groups	Number		Thin			Normal			Stout		
	Total	Per Cent	Number	Per Cent		Number	Per Cent		Number	Per Cent	
				Down	Across		Down	Across		Down	Across
16-29	142	26.0	43	38.0	30.3	84	26	59.0	15	14.7	10.7
30-39	150	28.0	31	27.0	20.7	98	30	65.0	21	20.6	14.3
40-49	107	19.7	20	17.5	18.7	66	20	62.0	21	20.6	19.3
50+	144	26.3	20	17.5	13.9	79	24	55.0	45	44.1	31.1
Total	543†		114	21.0		327	60.0		102	19.0	

* In this and the following tables, F means frequency, S. D., standard deviation, and P. E., probable error.

† This number is less than the 573 in the table above because the weight and height were not given in some of the records. A similar discrepancy will be found in other tables in this paper.

four age groups and the distribution curves were studied. As will be noted, the blood pressures were divided into class intervals of 10 mm each. Table 1 summarizes the results obtained.

Now when we get the mean of a particular distribution and wish to correct it for age differences we multiply it by a factor obtained by dividing the mean of the normal group by a mean obtained by adding together the products of the numbers in the different age groups of

the particular distribution and the corresponding means from the standard group of 573, and dividing by the total number in the particular distribution. In other words, we compare the mean of the standard group with the weighted mean of a theoretical group in which the pressures are standard but the age distribution different. The method is simply an adaptation of one used in standardizing death rates⁸. The arithmetic of the process will be shown a little further on in the paper, this will doubtless make things clearer than any amount of description.

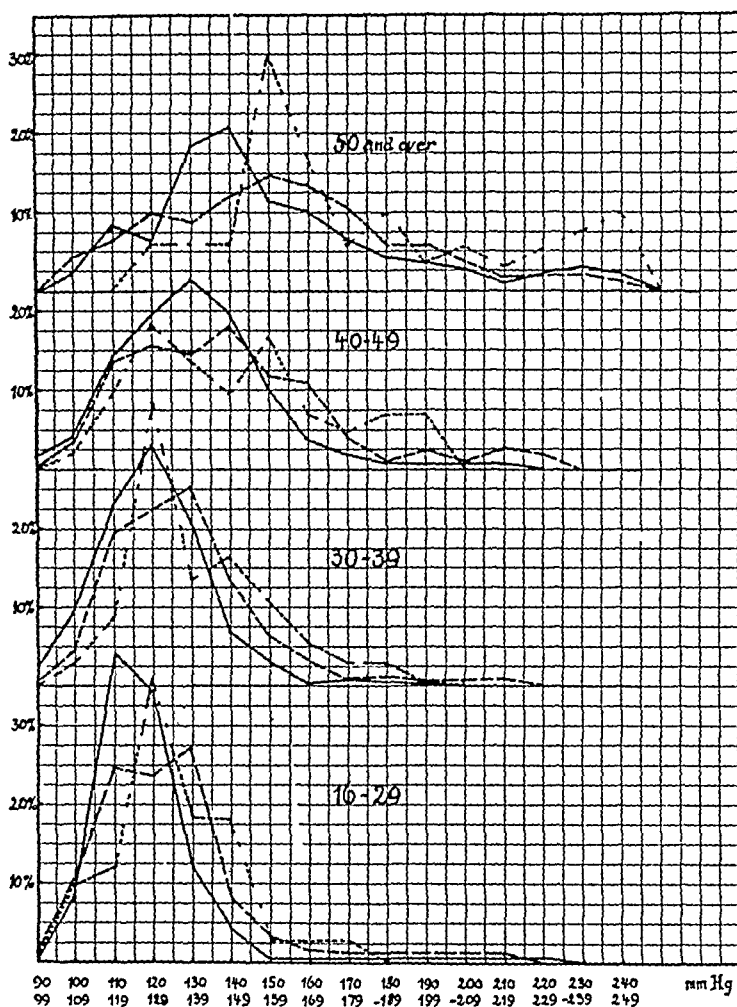


Chart 1—Distribution curves for women at different ages. the solid line represents the sexually normal, the broken line, the sexually abnormal plus, and the dotted line, the sexually abnormal double plus.

STANDARDS OF NORMAL

In table 1 we note that the mean pressures for the four age groups are 122.1 ± 0.8 , 125.8 ± 0.8 , 135.3 ± 1.2 , and 154.4 ± 1.7 . If we remove from the 16 to 29 year group the data from eight women whose pelvic organs were questionable, the mean becomes 120.0 ± 0.5 and the

⁸ Pearl, R. Introduction to Medical Biometry and Statistics, Philadelphia, W. B. Saunders Company, 1923, p. 198.

standard deviation 8.7 mm. If we remove from the 30 to the 39 group the readings from twelve women whose sexual status was similarly doubtful, that mean becomes 123.4 ± 0.8 and the standard deviation 13.9. These corrected figures are probably more trustworthy as standards of normal, but as it was impossible to arrive at definite and settled decisions as regards most of these borderline cases, we felt it best to abide by our first attempt at classification.

On turning to the last paper by one of us (W. C. A.), on the pressures of university freshmen, it will be noted that their readings averaged a little lower than those from the office patients here reported. The yearly means for the women between 16 and 30 ranged about 117, and for those between 30 and 40 they were about 119. These readings were taken, however, by the palpatory method which gives results from 5 to 10 mm. lower than those obtained with the auscultatory method. It appears, therefore, that the women coming to a physician's office whom we have classified as sexually normal have pressures at about the same level as those of their sisters attending the university.

It will be noted, again, that the normal pressure rises little in the twenties and thirties. The big rise comes in the forties and fifties. The rise in the mean with increasing age up to 40 seems to be due mainly to an upward shift of the mode, or peak of the distribution curve (fig. 1). After that it is due partly to a shift in the mode, and partly to an increase in the number of individuals with pathologic pressures. The increase in pathologic pressures is most striking in the women over 50.

THE CORRECTION OF THE DATA FOR DIFFERENCES IN WEIGHT

The need for an age correction factor in comparing the pressures of any two groups of women is obvious. The need for a correction factor for weight was not so obvious until we had prepared table 2. Then it became clear that it would be impossible to estimate the effect, let us say, of child-bearing on blood pressure, unless we could exclude the influence of the gain in weight which so often comes with pregnancy and lactation. We would either have to study a group of mothers who had preserved their antepartous weight or else we would have to use a correction factor for weight.

Symonds⁹ has published extensive tables showing the relation between blood pressure, age, and weight but like all the insurance statistics they have little significance for the clinician because they are based on the findings in a group of men and women who have been selected as conforming to certain already chosen standards. In other

⁹ Symonds, B. The Blood Pressure of Healthy Men and Women, *Proc. A. Life Ins. Dir. of America* 9:22, 1922.

words, the statistics are based only on the data from accepted risks, and the examiner, having fixed the range, practically fixes the means that later he presents to us as standards of normal. The clinician would be helped more if the insurance men would publish the data from all those whom they examine. Even then, we would not get a perfect sampling from the population because those who know that they have high pressures know the futility of applying for insurance.

Even the clinician at times succumbs to the temptation to exclude bothersome pathologic cases from his frequency distributions, but as it is impossible to know where to begin or where to stop in this deleting process, and as we want first to study disease as we find it, we have

TABLE 2—Standards for the Weight Correction

Blood Pressure	Age Groups														
	16-29			30-39			40-49			50+			All Ages		
	Thin	mal	Stout	Thin	mal	Stout	Thin	mal	Stout	Thin	mal	Stout	Thin	mal	Stout
90 to 99	1			5	3		2						6	3	9
100 to 109	15	13	2	5	15	2	3	5	1	4	1	23	37	6	66
110 to 119	30	53	7	22	35	9	12	22	3	5	9	2	69	119	21
120 to 129	23	45	16	23	61	13	8	28	9	5	13	3	59	147	41
130 to 139	19	30	11	15	50	12	11	28	9	7	20	7	52	128	39
140 to 149	3	16	4	3	27	7	5	33	10	4	21	13	15	97	34
150 to 159	1	3	1	6	12	3	2	19	8	2	24	17	11	58	29
160 to 169		3		2	5	1	4	11	6	4	16	12	10	35	19
170 to 179		2	1	1	3	1		5	5	3	10	7	4	20	14
180 to 189					2	1		2	3	1	9	8	1	13	12
190 to 199						2		5	1		2	7		7	10
200 to 209		1							1	1	8	3	1	9	4
210 to 219		1		1		1	3	2			2	2	1	6	5
220 to 229								1			1	1		1	2
230 to 239								1			5	1		6	1
240 to 249											3	4		3	4
Total	92	167	42	81	213	52	47	162	59	32	147	88	252	689	1182
Mean	120.7	126.3	128.3	126.9	129.8	136.0	128.5	141.4	151.3	143.6	157.3	166.6	127.0	137.5	149.6
S. D.	11.7	16.6	12.9	18.7	16.1	22.8	17.7	23.5	26.3	22.9	32.0	28.3	18.3	25.1	28.8
P. C. of mean	0.8	0.9	1.3	1.4	0.7	2.1	1.7	1.2	2.3	2.7	1.7	2.2	0.8	0.6	1.2
Percentage	30.5	55.5	14.0	23.5	61.5	15.0	17.5	60.5	22.0	12.0	55.0	33.0	21.3	58.1	20.6

Mean of 915 under 50 = 131.6 \pm 0.5Mean of 647 under 40 = 127.7 \pm 0.4

thought it best, at least for the present, to chart and to use all the data obtained.

In making table 2 it would probably have been better if we could have used only the data from the same sexually normal group which we used for the age standards, but that group, when divided into twelve parts, was hardly sufficient, and so we have used the data from 1,182 histories in which the record was full enough so that we could classify the individual as thin, normal or stout. The arithmetic involved in using the means of these smaller age and weight groups to correct the mean of a special distribution will be shown a little further on in the section on single and married.

In the larger distributions such as those of the "sexually abnormal" and those with abnormal hair or fibroids, we used the data in this table

to correct for age and for weight at the same time, but in the smaller groups we did not attempt to make the twelvefold classification and used instead a threefold one of thin, normal and stout. We then used in the calculation the means 127.0, 137.5 and 149.6, which are to be found in table 2, the age correction factor was obtained separately.

We see from these figures that the mean blood pressure increases 10 mm. as we pass from the thin to the normal and another 12 mm. as we pass from the normal to the stout. This is shown more graphically in figure 2. There it will be noted that in thin persons the big rise in blood pressure takes place late, that is, after 50. In the well proportioned and in the stout the rise is definite in the forties.

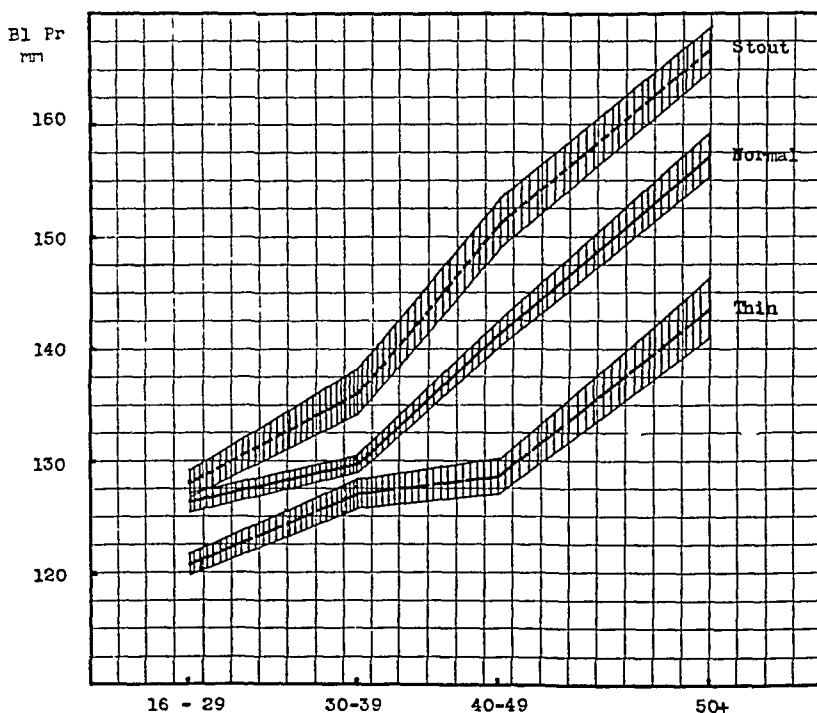


Chart 2—Mean systolic blood pressure in women with different builds and ages. The shaded area represents the \pm probable error of the mean.

The percentage composition of the different age groups according to weight, as shown at the lower end of table 2, is also of interest. As we all know, the weight of women tends to rise as they grow older. The percentage of well proportioned women seems to remain about the same from youth to old age.

SINGLE AND MARRIED

We next grouped the readings from single and married, the married including also the widowed, the divorced and the separated. Our idea was that a good many women might perhaps stay single because of sex deficiencies, mental and physical, and in that case we should, according

to our theory, find a greater number of high pressures among the single

Table 3 and figure 3 show the number of single and married in the different age groups. It will be noted from table 4 that 23.4 per cent of the sexually normal were single, and on turning to the 1920 census report, we find that 23.9 per cent of the women in California over 15 are single. Apparently, then, our group of normals is fairly representative of California women.

TABLE 3—Single and Married

Pressure Blood	25-29 Years				30-39 Years				40-49 Years				All Sin- gle	All Mar- ried
	Single		Married		Single		Married		Single		Married			
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent		
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent		
90 to 99					1	1.5	4	1.5			2	1.0	1	6
100 to 109	6	9.0	8	8.0	5	5.3	19	7.4			11	5.0	11	38
110 to 119	16	24.0	37	37.0	17	18.0	48	18.7			27	12.2	42	112
120 to 129	23	34.0	22	22.0	23	24.5	76	29.5	9	16.3	35	15.9	58	133
130 to 139	14	21.0	23	23.0	23	24.5	54	21.0	13	23.6	36	16.4	50	113
140 to 149	6	9.0	5	5.0	14	14.7	27	11.0	8	14.5	39	17.7	28	71
150 to 159	1	1.5	3	3.0	4	4.1	16	6.5	8	14.5	25	11.3	13	44
160 to 169	1	1.5			4	4.1	4	1.5			20	9.1	5	24
170 to 179			2	2.0	1	1.5	4	1.5	2	2.7	8	3.6	3	14
180 to 189					1	1.5	2	0.8			4	1.8	1	6
190 to 199					1	1.5			2	2.7	3	1.3	3	3
200 to 209							1	0.4	1	1.8	3	1.3	1	4
210 to 219								0.8			4	1.8		6
220 to 229											2	1.0		2
230 to 239														
240 to 249											1	0.5		1
Total	67		100		94		257		55		220		216	577
Mean	125.3		124.4		131.7		129.6		138.3		142.3		131.3	133.5
S. D.	12.4		13.8		17.5		18.3		20.6		26.0		17.7	22.0
P. E. of mean	1.0		0.9		1.2		0.7		1.9		1.2		0.8	0.6

Correction for age and weight: Single $131.3 \pm 0.8 \times 1.006 = 132.1 \pm 0.8$
 Married $133.5 \pm 0.6 \times 0.981 = 131.4 \pm 0.6$

TABLE 4—Percentages of Single, Married and Divorced

	Abnormal												Total	
	Normal			+		++								
	Num ber	Per Cent		Num ber	Per Cent		Num- ber	Per Cent		Num- ber	Per Cent			
		Down	Across		Down	Across		Down	Across					
Single	134	23.4	40.3	146	28.0	44.2	52	36.0	15.5	332	27			
Married and widowed	412	72.0	48.7	347	68.0	41.0	86	60.0	10.3	845	69			
Divorced and separated	27	4.6	54.0	17	4.0	34.0	6	4.0	12.0	50	4			
Total	573		46.8	510		41.7	144		11.5	1227				

When we divided the single and married groups each into three other groups according to our classification into sexually normal and abnormal, we found, as we expected, that there were many more single among the abnormals, especially in the earlier years. Most of the abnormals seem ultimately to get married, but they have to wait until their more sexual sisters have taken their pick of the available men.

Table 3 shows the distribution of the pressures in married and single women between the ages of 25 and 49. Women under 25 were excluded from consideration because one does not question a woman's being single in the years before that. We note, however, in the United States census report for 1920 that more than 70 per cent of the women in California are married by the time they are 25. We have excluded the women over 50 because most of them have had the menopause by that time and we would not expect to find a sexual factor still operative.

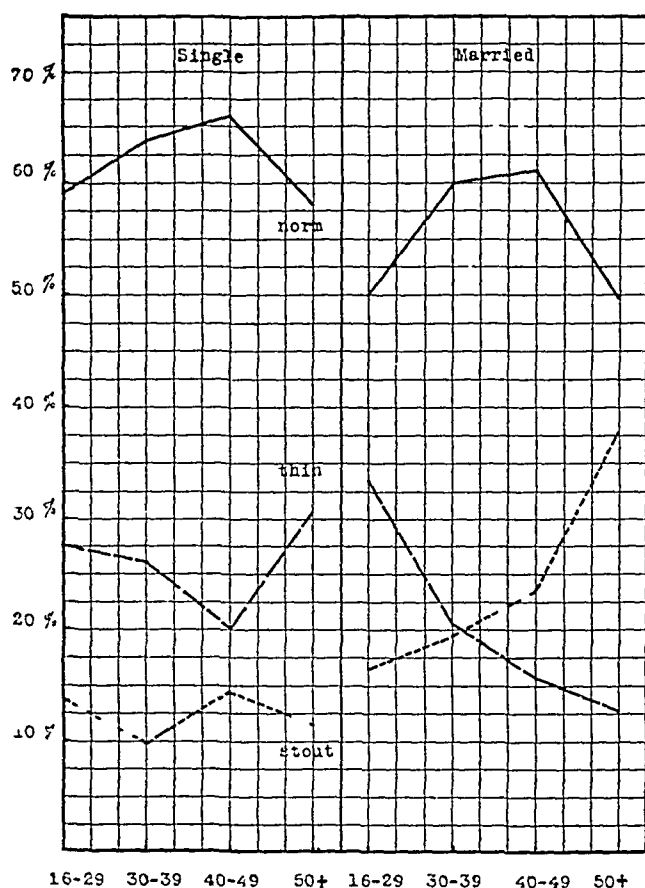


Chart 3—Percentage of thin, normal and stout women, single and married, and at different ages

When the two sets of distributions in table 3 are charted the curves show no definite differences. The mean of all the single women was 131.3 ± 0.8 , and of the married women 133.5 ± 0.6 . We note, however, in table 5 that there were nearly twice as many stout women among the married as there were among the single, so some correction had to be made for that. At the same time correction had to be made for the age differences. The arithmetic of the process is shown in the work sheet appended to the table.

TABLE 5—Body Build in Single and Married

Age Groups	Single								Married							
	Total	Thin		Normal		Stout		Total	Thin		Normal		Stout		Total	Total
		Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent		Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent		
25-29	65	21	32.3	37	57.0	7	10.7	101	27	26.7	57	56.4	17	16.9	175	175
30-39	82	20	24.4	54	66.0	8	9.6	261	45	17.2	166	63.6	50	19.2	461	461
40-49	51	11	21.5	30	59.0	10	19.5	215	32	14.9	131	61.0	52	24.1	408	408
Total	198	52	26.2	121	61.1	25	12.7	577	104	18.0	354	61.4	119	20.6	1037	1037

Build	Married			
	No Children		With Children	
	Number	Per Cent	Number	Per Cent
Thin	40	21.6 ± 2.0	113	20.0 ± 1.1
Normal	112	60.5 ± 2.4	302	53.5 ± 1.4
Stout	33	17.9 ± 1.9	150	26.5 ± 1.3

Appendix
To Correct for Age and Weight
Single

Age	Thin	Normal	Stout	Total
25-29	21 × 120.7 = 2534.7	37 × 126.3 = 4673.1	7 × 128.3 = 898.1	52 6486.2
30-39	20 × 126.9 = 2538.0	54 × 129.8 = 7009.2	8 × 136.0 = 1088.0	121 15924.5
40-49	11 × 128.5 = 1413.5	30 × 141.4 = 4242.2	10 × 151.3 = 1513.0	25 3499.1
	<hr/> 52	<hr/> 6486.2	<hr/> 121	<hr/> 15924.5
			<hr/> 25	<hr/> 3499.1
				<hr/> 198 25909.8

$$\frac{25909.8}{198} = 130.8$$

Normal mean from table 2, age 16-49 = 131.6

$$\frac{131.6}{130.8} = 1.006 = \text{correction factor}$$

Married

Age	Thin	Normal	Stout	Total
25-29	27 × 120.7 = 3258.9	57 × 126.3 = 7199.1	17 × 128.3 = 2181.1	101 13081.4
30-39	45 × 126.9 = 5710.5	166 × 129.8 = 21516.8	50 × 136.0 = 6800.0	354 47269.3
40-49	32 × 128.5 = 4112.0	131 × 141.4 = 18523.4	52 × 151.3 = 7867.6	119 16348.7
	104 13081.4	354 47269.3	119 16348.7	577 77199.4

$$\frac{77199.4}{577} = 133.8$$

$$\frac{131.6}{133.8} = 0.984 = \text{correction factor}$$

131.3 ± 0.8 × 1.006 = 132.1 ± 0.8 = corrected mean of the single
133.5 ± 0.6 × 0.984 = 131.4 ± 0.6 = corrected mean of the married

We see then, as we expected, that the pressures of the single women average a little higher than those of the married women. The difference is so small that if we did not know that there is more hypogonadism among the single, and that the hypogonads have definitely higher pressures, we would pay no attention to it. Ordinarily, we put little confidence in a difference unless it is three or four times its probable error. That figure is obtained as follows

$$132.1 \pm 0.8 - 131.4 \pm 0.6 = 0.7 \pm \sqrt{0.8^2 + 0.6^2} = 0.7 \pm 1$$

In this case the difference is actually less than its probable error¹⁰

TABLE 6—*Sexually Abnormal +*

Blood Pressure	Age Groups								All Ages Together	
	16-29		30-39		40-49		50+			
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent
90 to 99	1	0.7	1	0.6	1	0.8			3	0.6
100 to 109	14	10.2	7	4.3	4	3.4	4	4.3	29	5.7
110 to 119	33	24.2	32	19.7	17	14.3	6	6.5	88	17.2
120 to 129	32	23.4	36	22.4	18	15.2	9	9.8	95	18.7
130 to 139	37	27.0	40	25.0	17	14.3	8	8.7	102	20.0
140 to 149	11	8.0	22	13.7	21	17.7	11	12.0	65	12.7
150 to 159	5	3.6	11	6.8	14	11.8	13	14.1	43	8.5
160 to 169	2	1.5	5	3.1	13	10.7	12	13.1	32	6.3
170 to 179	1	0.7	2	1.2	5	4.2	10	10.9	18	3.5
180 to 189			2	1.2	1	0.8	6	6.5	9	1.8
190 to 199			1	0.6	2	1.7	6	6.5	9	1.8
200 to 209					1	0.8	3	3.7	4	0.8
210 to 219	1	0.7	2	1.2	3	2.5	1	1.1	7	1.4
220 to 229					2	1.7			2	0.4
230 to 239							2	2.1	2	0.4
240 to 249							1	1.1	1	0.2
Total	137	27.0	161	31.6	119	23.4	92	18.0	509	
Mean	126.8		132.9		143.4		156.8		138.1	
S. D.	16.0		19.2		26.2		30.1		20.7	
P. E. of mean	0.9		1.0		1.6		2.1		0.6	

Correction for age and weight All ages $138.1 \pm 0.6 \times 1.007 = 139.1 \pm 0.6$

Age Groups	Number		Thin		Normal		Stout	
	Total	Per Cent	Number	Per Cent		Number	Per Cent	
				Down	Across		Down	Across
16-29	131	27	29	33.3	22.1	79	26.7	60.3
30-39	155	32	33	38.0	21.3	92	31.0	59.4
40-49	117	24	17	19.5	14.5	79	26.7	67.5
50+	85	17	8	9.2	9.4	46	15.6	54.0
Total	488		87	17.6		296	60.6	
						105	21.8	

Figure 3 shows graphically the percentage of thin, normal and stout in all the women over 16, single and married. The striking difference between the two groups is to be found in the greater number of stout among the married women and particularly among the older married women. It is interesting to note also that the single women tend to get thin after 50 while their married sisters are getting fat. Apparently

¹⁰ Pearl (Footnote 8, p. 218)

the cartoonist's picture of the thin old maid rests on a firm biologic basis

When we divide the group of married women into those who have had children and those who have not, we find, as we would expect, that 26.5 ± 1.3 per cent of the child-bearing group are stout as compared with 17.9 ± 1.9 per cent in the nulliparous group. We find also that even the childless married women are a little heavier than their single sisters, only 12.7 ± 1.6 per cent of whom are stout.

 TABLE 7—*Sexually Abnormal* ++

Blood Pressure	Age Groups								All Ages Together	
	16-29		30-39		40-49		50+			
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent
90 to 99										
100 to 109	3	9.1	1	2.8	1	2.3			5	3.5
110 to 119	4	12.2	3	8.3	4	9.3			11	7.7
120 to 129	12	36.5	13	36.0	8	18.6	2	6.6	35	24.6
130 to 139	6	18.2	5	13.9	6	14.0			17	12.0
140 to 149	6	18.2	6	16.7	4	9.3	2	6.6	18	12.7
150 to 159	1	3.0	4	11.1	7	16.3	9	30.0	21	14.7
160 to 169			2	5.6	3	7.0	5	16.7	10	7.0
170 to 179	1	3.0	1	2.8	2	4.6	2	6.6	6	4.2
180 to 189			1	2.8	3	7.0	3	10.0	7	4.9
190 to 199					3	7.0	1	3.3	4	2.8
200 to 209							2	6.6	2	1.4
210 to 219					1	2.3	1	3.3	2	1.4
220 to 229										
230 to 239										
240 to 249					1	2.3	3	10.0	4	2.8
Total	33	23.2	36	25.3	43	30.3	30	21.2	142	
Mean	129.0		136.4		150.3		173.5		146.8	
S. D.	13.9		17.8		33.6		31.4		29.3	
P. E. of mean	1.6		1.9		3.4		3.8		1.7	

Correction for age and weight All ages $146.8 \pm 1.7 \times 0.980 = 143.9 \pm 1.7$

Age Groups	Number		Thin			Normal			Stout		
	Total	Per Cent	Number	Per Cent		Number	Per Cent		Number	Per Cent	
				Down	Across		Down	Across		Down	Across
16-29	29	21	6	33.3	20.7	16	20	55.0	7	17.0	24.3
30-39	35	25	6	33.3	17.1	24	30	68.6	5	12.2	14.4
40-49	43	31	3	16.7	7.0	24	30	56.0	16	39.0	37.0
50+	32	23	3	16.7	9.4	16	20	50.0	13	31.8	40.6
Total	139		18	13.0		80	57.5		41	29.5	

THE SEXUALLY ABNORMAL

In tables 6 and 7 we have analyzed the data from the women designated sexually abnormal, plus and double plus. As already pointed out, the first group contains the data from many doubtful cases in which it was hard to say where the line should be drawn. The second group is made up of women who were decidedly abnormal sexually. Figure 1 shows the distribution curves plotted from the data in tables 1, 6 and 7. These curves show the homogeneity of the data from the

younger women, the gradual shifting of the mode with age, and the marked spreading to the right in the later years. They show also the shifting of the whole distribution to the right (higher pressures) as we pass from the normal to the plus and again to the double plus.

After correcting the means of the plus and double plus groups for age and weight, we find that they are 139.1 ± 0.6 mm and 143.9 ± 1.7 mm, respectively. As we expected, these figures are much higher than that for the normals, which, as will be remembered, was 133.8 ± 0.7 mm. The differences here are so much larger than their probable errors that the chances are hundreds of millions to one that they mean something.

TABLE 8—Age Distribution of the Different Groups

Age Groups	All Together		Normal		Sexually Abnormal +		Sexually Abnormal ++		Fibroids		Masculine Hair Distribution	
	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
16-29	320	26.2 ± 0.3	150	26.1 ± 1.2	137	27.0 ± 1.3	33	23.2 ± 2.4	11	8.8 ± 1.7	65	36.3 ± 2.4
30-39	354	28.8 ± 0.3	157	27.4 ± 1.3	161	31.6 ± 1.4	36	25.3 ± 2.5	39	31.2 ± 2.8	58	32.4 ± 2.4
40-49	272	22.2 ± 0.3	110	19.2 ± 1.1	119	23.4 ± 1.3	43	30.8 ± 2.6	48	38.4 ± 2.9	38	21.2 ± 2.1
50+	278	22.8 ± 0.3	156	27.3 ± 1.3	92	18.0 ± 1.1	30	21.2 ± 2.3	27	21.6 ± 2.5	18	10.1 ± 1.5
Total	1,224		573	46.8 ± 0.3	509	41.6 ± 0.3	142	11.6 ± 0.2	125	10.2 ± 0.2	179	14.6 ± 0.2

Age Groups	Ovariectomy		Hysterectomy		Thyroid Small		Thyroid Slightly Enlarged		Thyroid Definitely Enlarged and Toxic	
	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent	Num-ber	Per Cent
16-39	44	50.1 ± 3.6	13	25.6 ± 4.2	246	55.0 ± 1.6	83	71.0 ± 2.8	42	53.0 ± 3.8
50+	43	49.9 ± 3.6	38	74.4 ± 4.2	202	45.0 ± 1.6	34	29.0 ± 2.8	37	47.0 ± 3.8
Total	87	7.1 ± 0.5	51	4.1 ± 0.4	448	36.6 ± 0.3	117	9.6 ± 0.6	79	6.4 ± 0.5

The next problem is to study separately the influence of the different forms of abnormality which we have lumped together as "sexually abnormal." As we shall see, some seem to have a marked effect on the blood pressure and others do not.

MASCULINE DISTRIBUTION OF BODY HAIR

On turning to table 9 we note that there were 179 cases in which this bodily peculiarity was mentioned in the records. Undoubtedly there were many more in which such hair was present in moderate amount and not commented on. As we shall note again later when we come to study figure 4, there is a strange absence of the older women from this group. Most of those observed with a pronouncedly masculine distribution of hair, especially on the abdomen, were in their twenties. It would seem either that such hair must fall out later or else that a considerable number of these women must die young.

There was an incidence of 14.6 ± 0.7 per cent for the whole group of 1,224. Studies that we hope to report later indicate that this peculiarity is found mainly in women who have an infantile type of uterus. There were eighteen women in the group with that type of uterus, and ten of them, or 56 ± 8 per cent had an abnormal distribution of hair. In the combined plus and double plus groups the incidence was 26.3 ± 1.2 per cent.

TABLE 9—*Masculine Distribution of Body Hair*

Blood Pressure	Age Groups								All Ages Together	
	16-29		30-39		40-49		50+			
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent
90 to 99					1	2.6			1	0.6
100 to 109	7	10.8	1	1.7	1	2.6			9	5.0
110 to 119	17	26.1	10	17.3	5	13.1		11.1	34	19.0
120 to 129	20	30.8	17	29.3	5	13.1	2	11.1	44	24.5
130 to 139	11	16.9	14	24.1	10	26.3	2	11.1	37	20.6
140 to 149	6	9.2	6	10.3	7	18.4	2	11.1	21	11.7
150 to 159	1	1.5	5	8.6	2	5.3	3	16.7	11	6.1
160 to 169	2	3.1	3	5.2	3	7.9	1	5.5	9	5.0
170 to 179	1	1.5					1	5.5	2	1.1
180 to 189					1	2.6	1	5.5	2	1.1
190 to 199			1	1.7	2	5.3	1	5.5	4	2.2
200 to 209							2	11.1	2	1.1
210 to 219			1	1.7	1	2.6			2	1.1
220 to 229										
230 to 239							1	5.5	1	0.6
240 to 249										
Total	65	36.3	58	32.4	38	21.1	18	10.1	179	
Mean	125.7		134.3		140.5		158.9		135.0	
S. D.	14.9		19.4		25.1		33.4		23.2	
P. E. of mean	1.3		1.7		2.8		5.3		1.2	

Correction for age and weight: All ages $135.0 \pm 1.2 \times 1.030 = 139.1 \pm 1.2$

Age Groups	Number		Thin			Normal			Stout		
	Total	Per Cent	Number	Per Cent		Number	Per Cent		Number	Per Cent	
				Down	Across		Down	Across		Down	Across
16-29	63	36.6	22	58.0	35.0	28	30.8	44.5	13	30.3	20.5
30-39	58	33.8	11	29.0	19.0	35	38.5	60.4	12	28.0	20.6
40-49	36	20.9	4	10.5	11.1	21	22.8	58.3	11	25.6	30.6
50+	15	8.7	1	2.5	6.7	7	7.9	46.7	7	16.1	46.7
Total	172		38	22.0		91	53.0		43	25.0	

It may easily be that in some of the cases the abnormal hairiness was due not so much to a deficiency in the ovarian secretion which restrains growth as to an oversupply of some factor that promotes growth. The fathers of a good many of these women were particularly hairy, and some of the daughters had unusually luxuriant growths of hair on the head, eyebrows, arms and legs. We have the impression, however, that in women, hairiness even on the arms and legs is a sign of hypogonadism. In a few cases the hairiness of the abdomen developed after a pelvic operation, but in no such case was it abundant.

Just as we would expect from our theory, these women whose ovarian development was so poor that a latent hairiness could emerge have high pressures. As will be seen from table 9, the mean was 139.0 ± 1.2 mm. Furthermore, if we plot the means for the four age groups, or if we plot the corresponding percentages with pressures over

TABLE 10—*Fibroids*

Blood Pressure	Age Groups								All Ages Fibroids Sure		All Ages (+ and ++) Fibroids Absent	
	16-29		30-39		40-49		50+		F	Per Cent	F	Per Cent
	F	Per Cent	F	Per Cent	F	Per Cent	F	Per Cent				
90 to 99			1	2.5	1	2.1	1	3.7	3	2.4	3	0.9
100 to 109			5	12.8	3	6.3	1	3.7	10	8.0	16	4.6
110 to 119	1	9.1	13	33.3	9	18.8	3	11.1	31	24.8	62	17.9
120 to 129	6	54.6	10	25.6	6	12.5	2	7.4	20	16.0	56	16.2
130 to 139	2	18.2	5	12.8	9	18.8	2	7.4	18	14.4	76	21.9
140 to 149	2	18.2	2	5.1	6	12.5	7	26.0	15	12.0	41	11.8
150 to 159			2	5.1	5	10.4	4	14.8	11	8.8	33	9.5
160 to 169			1	2.5	4	8.3	3	11.1	8	6.4	19	5.5
170 to 179							1	3.7	1	0.8	11	3.2
180 to 189					2	4.2	1	3.7	3	2.4	10	2.9
190 to 199					1	2.1			1	0.8	6	1.7
200 to 209					1	2.1			1	0.8	5	1.4
210 to 219									1	0.8	6	1.7
220 to 229												
230 to 239												
240 to 249					1	2.1	2	7.4	3	2.4	3	0.9
Total	11	8.8	39	31.2	48	38.4	27	21.1	125		347	
Mean	129.0		132.7		149.5		158.5		144.4		139.5	
S. D.	8.9		15.0		27.8		32.0		26.6		26.2	
P. E. of mean	1.8		1.6		2.7		4.1		1.6		0.9	

Correction for age and weight: Fibroids (all ages) $144.4 \pm 1.6 \times 0.983 = 142.0 \pm 1.6$
 No fibroids (all ages) $139.5 \pm 0.9 \times 0.983 = 137.1 \pm 0.9$

Age and Weight Distribution
Fibroids

Age Groups	Total		Thin		Normal		Stout	
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
16-29	19	9.3	7	36.8	9	47.3	3	15.9
30-39	63	30.8	20	31.7	34	54.0	9	14.3
40-49	80	39.2	10	12.5	55	69.0	15	18.5
50+	42	20.6	4	9.5	23	55.0	15	35.5
Total	204		41	20.0	121	59.3	42	20.7
No Fibroids								
16-29	121	33.3	30	24.8	70	58.0	21	17.2
30-39	110	30.2	26	23.5	66	60.0	18	16.5
40-49	69	19.0	13	18.9	37	53.6	19	27.5
50+	64	17.6	4	6.3	37	57.8	23	35.9
Total	364		73	20.0	210	57.7	81	22.3

130 or 140 mm., we see that the big difference between the normal and the hairy comes in the early years, and particularly in the thirties. After 50 there is little difference between the two groups. We find the same thing when we compare the data from the "normals" and the "one plus," and we will see it again when we come to analyze Plummer's figures on hyperplastic and nonhyperplastic goiter. With fibroids, the

big difference is found, as we might have expected, in the forties. Strange to say, in the "double plus" group the pressures continue to rise even in the fifties.

WOMEN WITH A FIBROTIC OR DEFINITELY FIBROID UTERUS

Table 10 shows the distribution of the data from these women. The high corrected mean, 142.0 ± 1.6 , indicates that these tumors have something to do with the production of hypertension. It may be, however, that in some cases the evenly enlarged fibrotic type of uterus is the result of hypertension and not its cause, or, more probably, they are both the result of some underlying diathesis.

As already pointed out, the greatest difference between the pressures of the normal and the fibrotic comes in the forties when the means are 135.3 ± 1.2 and 149.5 ± 2.7 , respectively.

Polak, Mittell and McGrath¹¹ once attempted to correlate hypertension and fibroid disease but as they did not use modern statistical methods and did not publish their frequency distributions it is impossible now to say what they got.

WOMEN WITH THYROID DISEASE

Table 11 gives a summary of the data from the women in the plus and double plus groups who had (1) no apparent thyroid disease, (2) who had somewhat enlarged thyroids, and (3) who had large or toxic thyroids. Unfortunately, some of the groups are pretty small, in spite of the fact that we grouped together women in ages 16-39 and 40-70.

The figures show that although the women with thyroid disease had pressures averaging considerably higher than normal, in the "sexually abnormal" group there was no significant difference between the pressures of those with and without thyroid disease. In a large proportion of the cases of thyroid disease the women had to be placed in the sexually abnormal group on account of severe disturbance of menstruation, pelvic disease, sexual anesthesia, etc. Doubtless the difference between the pressures of the normal and the plus group would have been more marked if we had not included with the latter so many women with enlarged but comparatively innocuous thyroids.

Fortunately, we have at our disposal Plummer's excellent study of the pressures in 1,728 women with nonhyperplastic goiter and 833 with hyperplastic goiter.¹² He does not give the data that would enable us to make the correction for weight but we can make the necessary

11 Polak, J. O., Mittell, E. A., and McGrath, A. B. What Is the Relation of Hypertension to Fibroid Disease of the Uterus? *Am J Obst & Gynec* 4:227 (Sept.) 1922.

12 Plummer, H. S. Blood Pressure and Thyrotoxicosis, *Tr A Am Phys* 30:450, 1915.

correction for age The corrected mean for the nonhyperplastic is 137.3, and for the hyperplastic, 151.0 mm. If the latter figure were corrected for weight, it would doubtless be still higher. As we have already noted in the section on abnormal haeminess, the big difference comes in the earlier years.

TABLE 11—Thyroid Disease

All cases taken from the plus and double plus groups

Blood Pressure	Thyroid Small		Thyroid Somewhat Enlarged		Thyroid Definitely Enlarged or Big and Toxic		All Ages		
	16-39		40-50+		16-39		Thyroid Not Enlarged	Thyroid Somewhat Enlarged	Thyroid Big and Toxic
	F	F	F	F	F	F			
From 90 to 99	1	1	1				2	1	
100 to 109	16	7	6	1	2		23	7	2
110 to 119	51	21	17	4	7	5	72	21	12
120 to 129	61	23	20	4	13	6	84	24	19
130 to 139	64	24	17	4	9	4	88	21	13
140 to 149	27	30	8	2	8	2	57	10	10
150 to 159	9	32	9	5	3	6	41	14	8
160 to 169	8	27	2	2		5	35	4	5
170 to 179	3	8	2	4		3	11	6	3
180 to 189	4	7		4		1	11	4	1
190 to 199		6		2		3	6	2	3
200 to 209		6					6		
210 to 219	2	4	1	1		1	6	2	1
220 to 229		1		1			1	1	
230 to 239		1				1	1		1
240 to 249		4					4		
Total	246	202	83	34	42	37	448	117	79
Mean	130.6	150.6	131.1	154.5	130.0	152.3	139.5	137.9	140.5
S. D.	18.0	29.9	19.2	30.4	13.0	29.6	26.0	25.4	25.0
P. E. of mean	0.8	1.4	1.4	3.5	1.3	1.3	0.8	1.5	1.8

Correction for age and weight

Thyroid normal

$$139.5 \pm 0.8 \times 1.005 \times 0.995 = 139.5 \pm 0.8$$

Thyroid somewhat enlarged

$$137.9 \pm 1.5 \times 1.032 \times 1.002 = 142.6 \pm 1.5$$

Thyroid big and toxic

$$140.5 \pm 1.8 \times 1.001 \times 0.994 = 139.8 \pm 1.8$$

Age Groups	Thyroid Small										
	Number		Thin			Normal			Stout		
	Total	Per Cent	Num- ber	Per Cent		Num ber	Per Cent		Num ber	Per Cent	
				Down	Across		Down	Across		Down	Across
16-39	216	52.5	50	69.5	23.1	126	52.0	58.4	40	41.3	18.5
40-50+	195	47.5	22	30.5	11.3	116	48.0	59.5	57	58.7	29.2
Total	411		72	17.5		242	59.0		97	23.5	
Thyroid Palpable or Slightly Enlarged											
16-39	91	62.0	24	75.0	26.5	53	59.0	58.0	14	56.0	15.5
40-50+	56	38.0	8	25.0	14.3	37	41.0	66.0	11	44.0	19.7
Total	147		32	21.8		90	61.2		25	17.0	
Thyroid Definitely Enlarged or Big and Toxic											
16-39	42	53.0	11	65.0	26.2	20	49.0	47.6	11	52.5	26.2
40-50+	37	47.0	6	35.0	16.0	21	51.0	57.0	10	47.5	27.0
Total	79		17	21.5		41	52.0		21	26.5	

We had some eighteen women with hypothyroidism, most of whom showed very high pressures. Their data are not tabulated here because of the smallness of the group. The fact that both hypothyroidism and hyperthyroidism are associated with hypertension shows that the increase

in pressure is due, not to changes in the amount of thyroxin, but to the primary disturbance which damages the gland one way or the other

WOMEN WITH ABNORMAL MENSTRUATION

It is hard to deal with the group with abnormal menstruation statistically because so many have difficulties in youth and no trouble later. Some begin to menstruate late, some have pain, some are irregular,

TABLE 12—Menstruation

Blood Pressure	Normal Menstruation		Abnormal Menstruation		Age 16-39	
	Age 16-29	Age 30-39	Age 16-29	Age 30-39	Normal	Abnormal
	F	F	F	F		
From 90 to 99	1	3	1	3	4	4
100 to 109	12	8	12	12	20	24
110 to 119	39	22	41	32	61	73
120 to 129	35	47	45	30	82	75
130 to 139	24	36	31	33	60	64
140 to 149	6	22	14	13	28	27
150 to 159	4	13	1	6	17	7
160 to 169	1	2	1	5	3	6
170 to 179	1	2	1	2	3	3
180 to 189		1			1	
190 to 199		1			1	
200 to 209		1			1	
210 to 219		1			1	
220 to 229						
230 to 239						
240 to 249						
Total	123	159	147	136	282	283
Mean	123.8	132.0	124.7	127.5	128.4	126.0
S. D.	13.4	18.5	12.7	16.3	17.0	14.6
P. E. of mean	0.8	1.0	0.7	0.9	0.7	0.6

Correction for age and weight $128.4 \times 1.000 \times 0.997 = 128.0 \pm 0.7$
 $126.0 \times 1.000 \times 1.003 = 126.5 \pm 0.6$

Age Groups	Menstruation Normal							
	Number		Thin		Normal		Stout	
	Total	Per Cent	Per Cent		Per Cent		Per Cent	
			Number	Down Across	Number	Down Across	Number	Down Across
16-29	114	43.5	31	52.0 27.0	68	43.0 60.0	15	33.3 13.0
30-39	148	56.5	29	48.0 19.5	89	37.0 60.0	30	66.6 20.5
Total	262		60	22.9	157	60.0	45	17.1
Age Groups	Menstruation With Difficulties							
	Number		Thin		Normal		Stout	
	Total	Per Cent	Per Cent		Per Cent		Per Cent	
			Number	Down Across	Number	Down Across	Number	Down Across
16-29	149	51.7	43	55.0 29.0	87	50.0 58.5	19	54.0 12.5
30-39	139	48.3	35	45.0 25.5	88	50.0 63.0	16	46.0 11.5
Total	288		78	27.0	175	61.0	35	12.0

some flow too little, others too much, others have psychic disturbances. It seemed impracticable to deal with so many small groups so we put them all together as shown in table 12. With the hope of bringing out differences more clearly we took only the women under 40. It will be seen that there is no significant difference between the mean pressures of the two groups with normal and abnormal menstruation. It is only 1.5 ± 0.9 mm.

SEXUAL ANESTHESIA

There were only sixty-four cases in which we had a record of this defect. This figure naturally does not give any idea of the incidence of this trouble as questions were not asked unless signs of hypogonadism were marked. It will be noted in table 13 that the mean pressure was 140.5 ± 1.7 mm, which is decidedly abnormal.

OVARIECTOMY AND HYSTERECTOMY

Table 14 shows that the women who have had severe operations on their pelvic organs have pressures that average higher than normal (137.0 ± 2.2 and 139.5 ± 3.3). Our impression is that this increase is due not so much to the operation as to the conditions that called for

TABLE 13—*Sexual Anesthesia*

Blood Pressure	Number	Per Cent	Blood Pressure	Number	Per Cent
From 90 to 99			From 170 to 179	1	1.6
100 to 109	5	7.8	180 to 189	1	1.6
110 to 119	7	11.0	190 to 199		
120 to 129	15	23.4	200 to 209	1	1.6
130 to 139	15	23.4	210 to 219		
140 to 149	11	17.2	220 to 229		
150 to 159	3	4.7	230 to 239		
160 to 169	5	7.8	240 to 249		
Total				64	
Mean					135.1
S. D.					19.6
P. E. of mean					1.6

Correction for age and weight $135.1 \pm 1.6 \times 1.040 \times 1.000 = 140.5 \pm 1.7$

Age Groups	Number	Per Cent	Build	Number	Per Cent
16 to 29	25	39.0 ± 4.1	Thin	13	20.0 ± 3.4
30 to 39	15	23.5 ± 3.6	Normal	39	61.0 ± 4.1
40 to 49	20	31.0 ± 3.9	Stout	12	19.0 ± 3.3
50 and over	4	6.5 ± 2.0			

it. It seemed to be higher in those who had begun life with poor pelvic organs than in those who had acquired them by the gonorrheal route.

EFFECTS OF PREGNANCY

Table 15 shows that when we exclude the influence of age and weight there is no difference between the pressures of women who have and who have not been pregnant.

EARLY OR LATE MENOPAUSE

In table 16 we have divided the women of 50 years and over into two groups, one in which the menopause had occurred before 50, and the other in which it had either occurred after 50 or had not yet appeared. As will be seen, there is no significant difference between the mean pressures of the two groups.

We have records of two interesting women one, aged 40, with a spontaneous menopause at 20 and a blood pressure of 110 systolic, 75 diastolic, the other is 27, with an operative menopause at 17 and a blood pressure of 134 systolic, 85 diastolic. Much apparently depends on the inheritance.

TABLE 14—*Ovariectomy and Hysterectomy**

Blood Pressure	Ovariectomy		Hysterectomy		All Ages	
	Age 16-39	Age 40-50+	Age 16-39	Age 40-50+	Ovariec- tomy	Hysterec- tomy
	F	F	F	F		
From 90 to 99						
100 to 109	5	3		2	8	2
110 to 119	13	1	4	5	14	9
120 to 129	12	6	3	5	18	8
130 to 139	5	7	3	1	12	4
140 to 149	5	7	2	6	12	8
150 to 159	1	5		9	6	9
160 to 169		4		2	4	2
170 to 179	1	3	1	1	4	2
180 to 189	1	2		2	3	2
190 to 199		3		1	3	1
200 to 209						
210 to 219	1	1			2	
220 to 229						
230 to 239				1		1
240 to 249		1		3	1	3
Total	44	43	13	38	87	51
Mean	127.9	151.0	130.6	153.5	139.3	147.6
S. D.	21.5	29.5	16.4	37.4	27.6	34.8
P. E. of mean	2.1	3.0	1.5	4.1	2.2	3.3

Correction for age and weight $139.3 \times 0.997 \times 0.987 = 137.0 \pm 2.2$
 $147.6 \times 0.956 \times 0.939 = 139.5 \pm 3.3$

Ovariectomy (+ and ++)											
Age Groups	Number		Thin			Normal			Stout		
	Total	Per Cent	Num ber	Per Cent		Num ber	Per Cent		Num ber	Per Cent	
				Down	Across		Down	Across		Down	Across
16-39	40	49 0	7	78 0	17 5	25	48 0	62 5	8	38 0	20 0
40-50+	42	51 0	2	22 0	48 0	27	52 0	64 0	13	62 0	31 0
Total	82		9	11 0		52	63 5		21	25 5	
Hysterectomy (+ and ++)											
16-39	13	29 0	6	86 0	46 0	6	23 0	46 0	1	8 3	8 0
40-50+	32	71 0	1	14 0	3 1	20	77 0	62 5	11	91 7	34 4
Total	45		7	15 5		26	58 0		12	26 5	

* Ovariectomy includes removal of ovarian cysts, hysterectomy includes total and partial hysterectomy.

We had several opportunities to observe the big rise that, as is well known, sometimes appears at the menopause. One woman went from 155 to 200 mm., another from 105 to 150, another from 145 to 205, and another from 160 to 220. We encountered a few cases, however, in which the pressure actually dropped during and after the change, and we saw many, of course, in which there was no striking change.

THE AGE COMPOSITION OF THE DIFFERENT GROUPS

Table 8 and figure 4 show us the age composition of the different groups that we have been studying, and from that we can get some idea of the time of life when the various disturbances or abnormalities appear. Thus, we are not surprised to find that most of the women in whom fibroids were discovered were in their thirties and forties, but we

TABLE 15—*Pregnancy and Child-Bearing, All Ages*

Blood Pressure	No Children		Children and Pregnancies	
	F	Per Cent	F	Per Cent
From 90 to 99	1	0.5	6	1.0
100 to 109	11	5.8	30	5.3
110 to 119	37	19.7	89	15.7
120 to 129	42	22.3	102	18.0
130 to 139	35	18.6	98	17.3
140 to 149	21	11.2	81	14.3
150 to 159	13	6.9	57	10.0
160 to 169	12	4.4	29	5.1
170 to 179	5	2.6	22	3.9
180 to 189	5	2.6	14	2.5
190 to 199	2	1.1	6	1.0
200 to 209			14	2.5
210 to 219	1	0.5	7	1.2
220 to 229	1	0.5	4	0.8
230 to 239			4	0.8
240 to 249	2	1.1	4	0.8
Total	188		567	
Mean	135.9		140.8	
S. D.	25.7		27.9	
P. E. of mean	1.3		0.8	

Correction for age and weight $135.9 \times 1.011 \times 1.003 = 137.8 \pm 1.3$ $140.8 \times 0.991 \times 0.992 = 138.4 \pm 0.8$

Age Groups	Total		No Children			Children and Pregnaneles		
	Num ber	Per Cent	Num ber	Per Cent		Num ber	Per Cent	
				Down	Across		Down	Across
16-29	132	17.5	46	24.5	34.8	86	15.2	65.1
30-39	235	31.2	55	29.2	23.5	180	31.7	76.5
40-49	181	24.0	50	26.6	27.5	131	23.1	72.5
50+	207	27.3	37	19.7	17.9	170	30.0	82.1
Total	755		188	25.0		567	75.0	
Builld								
Thin	153	20.0	40	21.6	26.0	113	20.0	74.0
Normal	414	55.4	112	60.5	27.0	302	53.5	73.0
Stout	178	24.6	33	17.9	18.0	150	26.5	82.0
Total	750		185	25.0		565	75.0	

are puzzled to note that most of the women with a masculine distribution of body hair were under 30. What happens to them after that? Do they die or does the hair fall out? This is a question that will be of interest to the medical directors of life insurance companies.

We see that in the later years of life the curve for the sexually normal parallels that for all the women in California (fourteenth census, 1920). In the early twenties, when young bodies tend to be strong and well, an internist does not see a full representation from the women

in his community, but the quota is more than made up in the thirties. Strange to say, there does not seem to be any increase in the incidence of disease in the years after 50. Apparently when final disease and death come they disable these older people so swiftly that few of them are able to visit a downtown consultant.

It is hard to explain the marked difference in the age composition of the plus and the double plus groups. One has its high peak in the

TABLE 16—*Menopause in Women Aged 50 and Over*

Blood Pressure	Age			
	Below 49		50-59	
	F	Per Cent	F	Per Cent
From 90 to 99				
100 to 109	3	2.7	1	1.0
110 to 119	7	6.4	4	4.1
120 to 129	7	6.4	5	5.1
130 to 139	12	10.9	15	15.3
140 to 149	15	13.6	12	12.2
150 to 159	18	16.4	20	20.7
160 to 169	9	8.2	13	13.1
170 to 179	9	8.2	10	10.2
180 to 189	8	7.3	5	5.1
190 to 199	5	4.5	2	2.0
200 to 209	7	6.4	5	5.1
210 to 219	2	1.8		
220 to 229	2	1.8		
230 to 239	2	1.8	2	2.0
240 to 249	3	2.7	3	3.0
260+	1	0.9	1	1.0
Total	110	53.0	98	47.0
Mean	162.0		160.5	
S. D.	34.1		31.4	
P. E. of mean	2.1		2.2	

$$\begin{aligned} \text{Correction for weight } 162.0 \times 1.001 &= 162.2 \pm 2.1 \\ 160.5 \times 0.997 &= 160.0 \pm 2.2 \end{aligned}$$

Age Groups	Number		Thin			Normal			Stout		
	Total	Per Cent	Per Cent			Per Cent			Per Cent		
			Num-ber	Down	Across	Num-ber	Down	Across	Num-ber	Down	Across
Menopause under 49	106	54.0	11	55.0	10.4	63	57.0	59.4	32	48.5	30.2
Menopause, 50 to 59	90	46.0	9	45.0	10.0	47	43.0	52.0	34	51.5	38.0
Total	196		20	10.2		110	56.0		66	33.8	

thirties and the other in the forties. The relatively small number of old women in both groups suggests a mortality rate higher than that for the normals, and that is probably the case. Their greater susceptibility to hypertension alone would give them a shorter expectancy of life. It might be noted here, however, that women seem to tolerate high pressures much better than men. Our impression is that they have fewer symptoms and that they live longer than men with similar pressures.

DIASTOLIC PRESSURE

In this paper we have confined our attention for the most part to a consideration of the systolic pressure because it seems to be the more interesting one. It is easier to measure and it has a wider range. The variations in the diastolic pressure are rather small as compared with the error inherent to the technic.

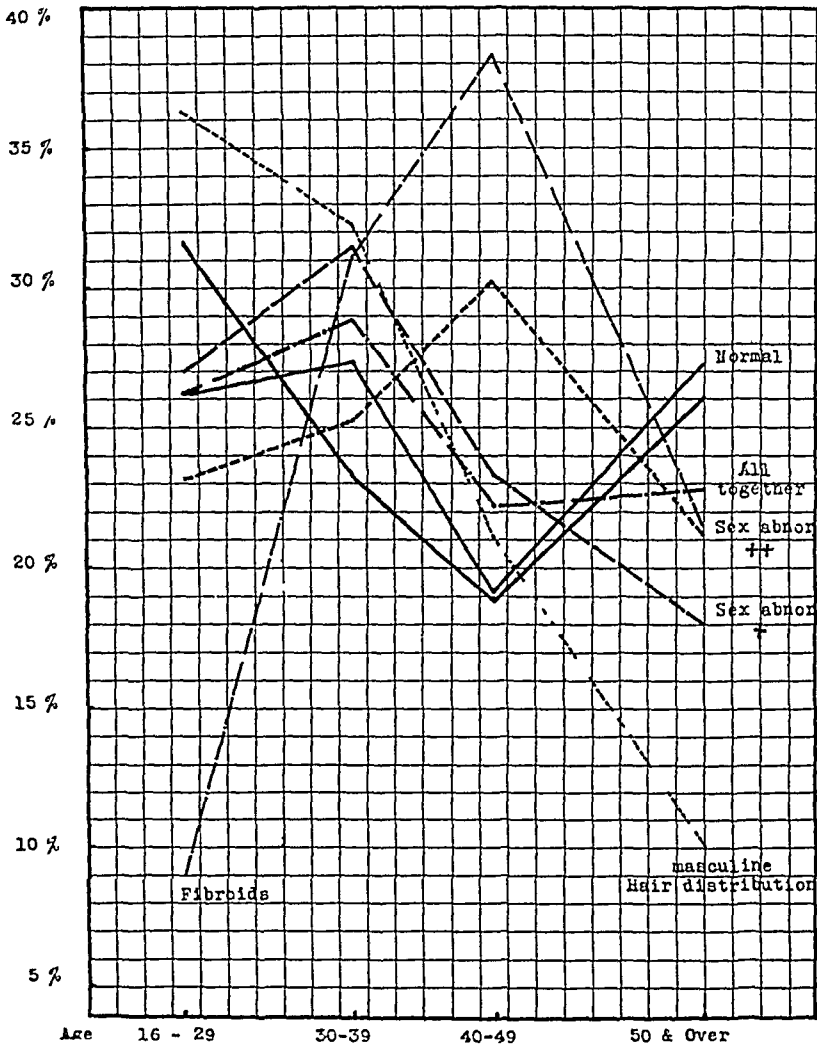


Chart 4—Age distribution of the different groups of women studied. The double line represents the distribution of the women in California over 16.

Table 17 shows the distribution of the diastolic pressures in the normal and in the combined plus and double plus groups. The means are shown graphically in figure 5, and it will be seen that they are higher in the sexually abnormal just as the systolic pressures are. The difference between the two means is ten times its probable error, which makes it almost certainly significant in spite of the fact that we have not calculated age and weight corrections.

COMMENT

We have seen now that women with poor ovaries are likely, early in life, to develop hypertension. The next question is: Do they ever get it early when they have good ovaries? By early we mean in the years before 30. The answer is probably yes, and we will do well now and in the future to concentrate our attention on these exceptions to the rule. As Darwin once pointed out, we can learn more from the study of troublesome exceptions than from anything else, so we will turn back and review carefully the records of the women under 30 who had hypertension, but who, in the original classification, were placed with the normals. Before we do this we will analyze briefly a couple of interesting cases seen since the present work was begun.

TABLE 17—Diastolic Pressure in Normal, + and ++

Blood Pressure	Age 16-29		Age 30-39		Age 40-49		Age 50+		All Ages	
	Normal F	+ and ++ F	Normal F	+ and ++ F	Normal F	+ and ++ F	Normal F	+ and ++ F	Normal F	+ and ++ F
40 to 49	1								1	
50 to 59	5	1		1					5	2
60 to 69	48	6	8	8	3	2	3		62	16
70 to 79	51	41	39	28	15	19	20	10	125	98
80 to 89	18	53	62	70	39	39	42	31	161	193
90 to 99	3	40	24	51	33	51	37	28	97	170
100 to 109	1	7	8	19	9	18	28	23	46	67
110 to 119		1		3	3	8	14	11	17	23
120 to 129				3		7	4	5	4	15
130 to 139		1				3	1	2	1	6
140 to 149	1			1			2	3	3	4
150+								3		3
Total	129	150	141	184	102	147	151	116	522	597
Mean	82.0	84.9	83.5	88.2	88.3	93.5	93.9	98.8	84.7	90.7
S. D.	11.1	10.9	9.4	12.4	10.3	14.1	14.9	18.0	14.3	14.9
P. E. of mean	0.8	0.6	0.6	0.6	0.7	0.8	0.8	1.1	0.4	0.4

The first is that of a girl of 19, with a pressure of 250 systolic, 150 diastolic. She was apparently well until two months before she came to us, when she developed an acute glomerulonephritis, with nitrogen retention, pulse of 120, metabolism of plus 34 per cent, and a large heart. She was finely built, her pelvic organs seemed normal, and there was nothing to suggest a sexual abnormality unless the hyperthyroidism. Strange to say, there was no history of infection past or recent to account for the nephritis. There were no dead teeth, the tonsils were well removed at the age of 9, and the appendix was removed for slight symptoms nearly two years before our examination. The fact that as long as she can remember she has gotten up once or twice at night to urinate indicates that she has carried poor kidneys from early childhood or perhaps even from birth.

Another girl of 17 had a pressure of 220 systolic, 160 diastolic. She also had a nephritis with nitrogen retention, severe headache, ocular changes and drowsiness. A brother died in childhood with the same condition. Again, there was no history of infection to explain the nephritis.

Mrs. C., aged 25, had a blood pressure of 220 systolic, 140 diastolic. She was finely built and sexual enough to have two illicit pregnancies at 19 and 20. Criminal abortions left her with considerable pelvic infection and probably a pus

tube It is a question whether or not she should be placed with the normals Our impression was that her ovaries were still normal and that, like the preceding two girls, she had the nephritic type of hypertension

Miss G, aged 23, had a blood pressure of 178 systolic, 120 diastolic She had inflammatory rheumatism at 19, dropsy at 12, a criminal abortion at 21, followed by some pelvic trouble and leukorrhea ever since, a big heart with a loud murmur and a large albuminuria Here again we had a nephritic hypertension based on severe infectious damage in childhood Her pelvic organs probably were damaged too

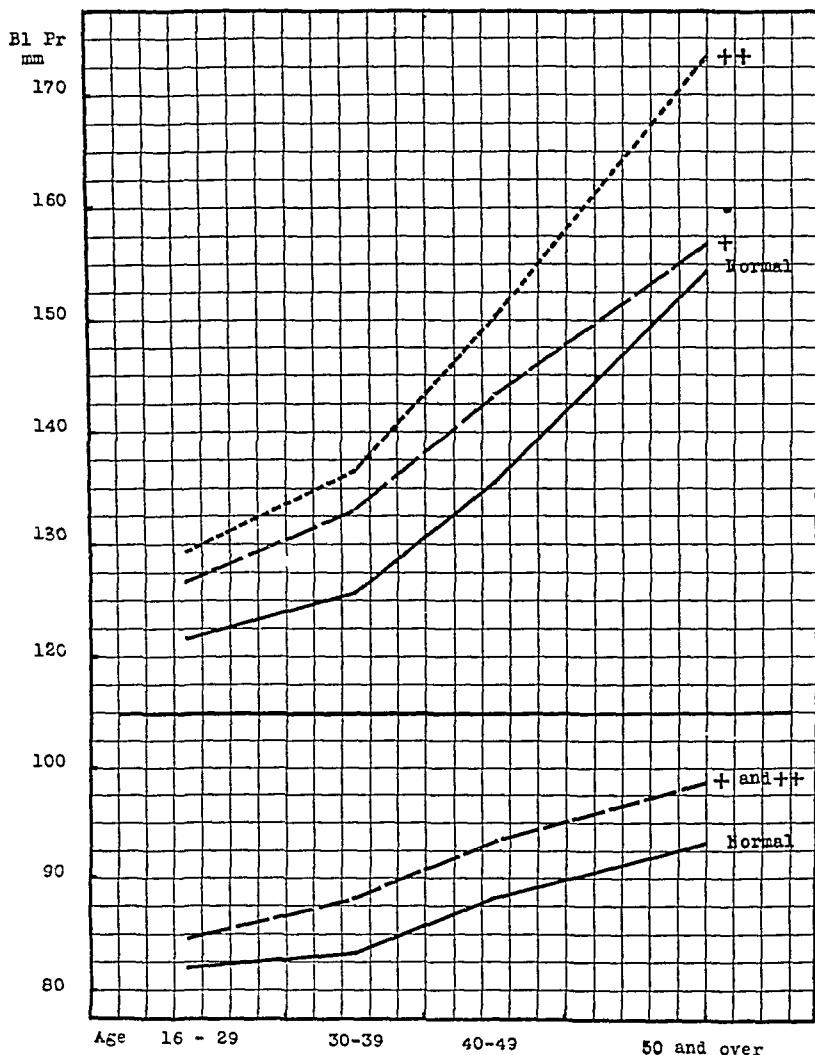


Chart 5—Mean blood pressure, systolic and diastolic, at the different ages, and in the sexually normal and abnormal groups

Mrs B, aged 28, had a blood pressure of 150 systolic, 95 diastolic Dr T Addis found a marked impairment of kidney function and she developed a pressure over 200 during pregnancy Her physical development showed some male characteristics and it might easily have been that her ovaries were insufficient, but primarily she seemed to have renal arteriosclerosis

If we turn now to a consideration of the seven women under 30 with pressures between 140 and 149, we find several whose ovaries may have been abnormal but who are certainly hard to classify One had a double tubal pregnancy and

now has a questionable left ovary and some hyperthyroidism. Another has been irregular in her menstruation and is somewhat hypothyroid. Another has considerable arteriosclerosis, she flows to excess and has had curettements. Another when seen was dying with a huge liver filled with metastases from a carcinoma of the anal ring. The necropsy showed normal pelvic organs. Another had an anteflexed, retroposed uterus. In addition she was a nun. Another seemed to be normal except for painful menstruation. At 18 she was already having illicit sexual relations. The seventh, so far as we could see, was normal sexually.

The impression we get from all this is that when we find a blood pressure over 150 mm. in a well sexed woman under 30, it is probably not an essential hypertension, or hypeipiesis, but is due to a nephritis or arteriosclerosis. It seems probable that some of those with pressures between 130 and 150 have the primary type of hypertension in spite of the fact that they have normal pelvic organs, but more careful studies will have to be made on the individuals in this group. It may also be

TABLE 18—Summary

	Corrected Mean
1,182 sexually normal and abnormal	137.7 \pm 0.5
573 sexually normal	133.8 \pm 0.7
509 sexually abnormal plus	139.1 \pm 0.6
142 sexually abnormal double plus	143.9 \pm 1.7
179 with masculine body hair	139.0 \pm 1.2
125 with fibroids	142.0 \pm 1.6
117 with somewhat enlarged fibroids	142.6 \pm 1.5
79 with large or toxic thyroids	139.8 \pm 1.8
64 with sexual anesthesia	140.5 \pm 1.7
51 with partial or total hysterectomy	139.5 \pm 3.3
87 with unilateral or bilateral ovariectomy	137.0 \pm 2.2
188 with no pregnancies	137.8 \pm 1.3
567 with children	138.4 \pm 0.8
216 single between ages of 25 and 49	132.1 \pm 0.8
577 married between ages of 25 and 49	131.4 \pm 0.6
282 with normal menstruation, between 16 and 39	128.0 \pm 0.7
283 with difficult menstruation, between 16 and 39	126.5 \pm 0.6
110 over 50 with menopause past	162.2 \pm 2.1
98 over 50 still menstruating	160.0 \pm 2.2

that such pressures are within the range of normal for a few women. Often they seem to produce no symptoms.

A study of those between 30 and 40 with high pressures shows, again, very few who seem to be perfectly normal. One, aged 36, with a pressure of 205 systolic, was placed with the normals because the only questionable thing about her pelvic organs was some slight enlargement and hardening of the uterus. It was the sort of thing that we could not be sure about. Another with a pressure of 194 systolic, 120 diastolic, was a fine looking woman with normal appearing pelvic organs—seen during an appendectomy. The only thing against her is her celibacy. Another with pressures of 170 systolic, 105 diastolic, seems to be perfectly normal sexually. Another with 150 systolic pressure is apparently sterile and has a somewhat enlarged thyroid, an enlarged uterus and dyspareunia. She should have been put in the plus group.

Our impression from studying the rest of the women in the 30 to 39 group with high pressures is that there are quite a few who began life with normal pelvic organs, but who are already, at this age, losing some of their ovarian strength, enough so that the latent tendency to hypertension can emerge

SUMMARY

Table 18 will enable the reader to compare quickly the means obtained in the different groups

We have seen that the average pressure for all ages in women who seem to be sexually normal is 134.5 ± 0.7 mm of mercury. Corrected for weight it is 133.8 ± 0.7 mm. The average in the twenties is 122.1 ± 0.7 , in the thirties it is 125.8 ± 0.7 , in the forties it is 135.3 ± 1.2 , and after 50 it is 154.4 ± 1.7 mm.

The mean diastolic pressure for the corresponding age groups is 82 ± 0.8 , 83.5 ± 0.6 , 88.4 ± 0.9 and 93.8 ± 0.9 .

Well proportioned women have systolic pressures that average 10 mm higher than those of the thin, and pressures in the stout average 12 mm higher than in the well proportioned. An allowance has to be made for these differences when any two groups of women are being studied.

The sexually abnormal have pressures that average considerably higher than do those of the sexually normal. As the sexually abnormal tend to get married a little late as compared with their normal sisters, we find that single women have pressures averaging a little higher than those of the married women.

A masculine distribution of body hair, sexual anesthesia, fibroids of the uterus, thyroid disease, and pelvic conditions requiring ovariectomy or hysterectomy are associated with high average pressures.

Abnormal menstruation, early menopause and pregnancy have no demonstrable effect.

Marked hypertension was found in a few girls who seemed to be normal sexually, but in these cases it was not of the primary type but was associated with severe forms of nephritis.

The evidence here presented supports the theory that the "essential" type of hypertension is a bodily peculiarity, inherited equally by girls and boys, but ordinarily repressed in women before the menopause by the ovarian or other related secretions. When the pelvic organs are subnormal, the disease may appear in women as early as it does in men.

We wish here to express our indebtedness to Dr. Raymond Pearl, who has so kindly come to our rescue in times of perplexity and who has gone over our manuscript. We wish also to thank Drs. R. L. McCalla, W. C. Frey and R. Franzen for help given along the way.

EXOPHTHALMIC GOITER

A FOLLOW-UP STUDY OF CASES TREATED WITH THE ROENTGEN
RAY¹

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Radiotherapy has been used in the treatment of hyperthyroidism for many years. The best controlled series of cases heretofore reported was that of Means and Aub¹ from the clinic of the Massachusetts General Hospital. Since then it has been increasingly popular as a means of treatment until at the present time it is being employed in many of the larger clinics throughout the country to depress the activity of thyroid glands that are producing a thyrotoxicosis. To the patient it offers a simpler, less hazardous, and more accurately controllable procedure than does surgery, with an equally good prognosis, and as a means of treatment deserves more universal usage. Only the overwhelming statistics from surgical clinics have kept it from advancing more rapidly.

The literature abounds in statistical studies of cases of exophthalmic goiter in which operations have been performed, but the results reported are either immediate results or follow-ups based on questionnaire postals or letters, which at best, with intelligent patients, is far from ideal. A personal follow-up, in which the operator or his assistant sees the patient at intervals of every six months or so for a number of years after the operation is the only way by which we can really judge the outcome of a disease. And this is not possible in large series, especially when many patients come from a distance. Hence it has seemed to me that an insight into the result of therapy and the ultimate prognosis of the disease could be gained by personal study of a small group of cases, and it is such a group of cases that are reported here.

These patients were all seen at the Presbyterian Hospital, either in the outpatient department or in the wards, and subsequently in the follow-up clinic. A secret in the success of keeping the follow-up material up to date was the fact that the patients always saw the same physician. Each felt that a personal interest was being taken in his case. This, by the way, is the secret of any successful follow-up clinic and works to the mutual benefit of physician and patient, prognosis and cure.

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¹ Means, J H, and Aub, J C. Basal Metabolism in Exophthalmic Goiter, Arch Int Med 24 645 (Dec) 1919.

At the outset of these studies every lead was investigated with the hope that some group characteristics might throw certain cases together and give us some lead as to therapy. For this purpose creatin metabolism, glucose mobilization, basal metabolism and electrocardiographic studies were made in addition to careful physical examination, blood counts and the usual hospital work up. As these gave no distinct criteria, clinically similar cases varying so strikingly in these special studies, we abandoned them and came to rely on a careful clinical work up and basal metabolic studies. This great variation in apparently similar cases must become apparent to anyone who studies hyperthyroidism carefully, and must impress him with the protean characteristics of the disease. Surely hyperthyroidism as we see it in exophthalmic goiter is not a dystrophy of the thyroid gland alone. One case will manifest its chief symptoms myocardially, another outwardly of the same intensity will affect the nervous system primarily, others will pick out the gastro-intestinal tract, and some will combine any or all of these symptom complexes. It is not uncommon to have the patient come to the clinic with the exophthalmos as the chief complaint. One patient came in because of breathlessness and irregular pulse. He was fibrillating owing to a full blown exophthalmic goiter, yet his myocardial symptoms were the only things that caught the focus of his attention. Another patient came in complaining of large tonsils. She had an outstanding exophthalmos and a severe exophthalmic goiter, but none of her complaints were referable to this.

Before going into the case reports, it seems logical to take up systematically some of the features that this series of cases have revealed. Psychoses have been comparatively rare, occurring only in three cases, one of which, following a mental shock, ran a rapid downhill course terminating in a schizophrenic state and death, in spite of intensive therapy. They all were in the nature of anxiety neuroses. Restlessness that sometimes simulates a severe chorea is not uncommon. The psychosis usually clears up under therapy.

Exophthalmos is one of the most puzzling features of the disease. No satisfactory explanation of its mechanism has yet been advanced. Why it should occur in the exophthalmic goiter syndrome and not in the adenoma complex is a mystery. It is one of the earliest signs and is one of the last to disappear after recovery. In some cases it continues to a greater or less degree permanently even after recovery.

Focal infection, especially localized in the tonsils, is common. The procedure in such cases is to eliminate the focus of infection at the same time the disease is being treated. In a few of our cases the tonsils were radiated as well as the thyroid gland, with quite an amazing shrinking of the hypertrophied tonsillar tissue. One unpleasant sequela of radiating the tonsils is an acute parotitis. Apparently the roentgen

may can cause a nonseptic inflammation of the salivary glands. This is not a serious complication, but it is quite uncomfortable and is to be avoided when possible.

As to the thyroid gland itself, there is no relation between its size and the severity of the thyrotoxicosis. The almost impalpable glands can cause the severest toxemia, while the largest sometimes show the least functional derangement. The best index here to the severity of the disease is the vascularity of the gland as manifested by large, palpable arteries, thrills and bruits. The consistency of the gland and the presence or absence of nodules is of minor importance. Substernal thyroids and persistent thymus glands are rare as judged by this series of cases, none having been discovered in any of the cases in which they were suspected and subsequent roentgenograms taken.

The heart is almost universally affected by the thyrotoxicosis. In only one or two cases of severe exophthalmic goiter was the pulse comparatively slow, from 80 to 90 to the minute. Tachycardia was a general finding. It is difficult to believe that any real organic change takes place in the myocardium, except perhaps in very toxic cases, or in long standing cases with persistent tachycardia. The majority of the patients treated with benefit show no evidence of any permanent damage to the myocardium. A not uncommon finding in the overactive thyrotoxic heart is a booming first sound with a suggestion of a presystolic rumble that resembles closely a mitral stenosis. This impurity has disappeared in the patients that have recovered clinically and metabolically. Fibrillation is not rare, having occurred in six cases of this series. Of these, three have been restored to normal rhythm, two after long standing fibrillation. Of the patients that have continued to fibrillate after recovery from hyperthyroidism, none have shown any signs of decompensation up to the present time. One was brought into the wards for quinidine therapy, but normal rhythm could not be established. Occasionally the toxemia is so severe that necrosis of the myocardium occurs. Goodpasture² has recently reported two cases of this condition. A high arterial pulse pressure is almost the universal finding. It is usually due to a slight increase in the systolic pressure and a greater decrease in the diastolic pressure. This is not an unusual finding in an overactive heart with a peripheral vasodilation.

In the liver focal necrosis must occur at times, though there is little evidence of this in the literature. Experimentally, it has been shown by Cramer³ and his collaborators that thyroid fed mice at necropsy show almost a total absence of liver glycogen, whereas control animals

² Goodpasture, E. W. Myocardial Necrosis in Hyperthyroidism, *J. A. M. A.* **76** 1545 (June 4) 1921.

³ Cramer, W., and Krause, R. A. *Proc. Roy. Soc., Sec. B*, **86** 50, 1913.

have the usual amount, some work by me⁴ on the glucose mobilization rate in exophthalmic goiter tends to confirm this in human beings. Patients with hyperthyroidism when given glucose burned it with great readiness, but were unable to store it with anything like the usual rapidity of the normal control, and therefore had high blood sugar and a transient glycosuria. This perhaps is the reason that certain hyperthyroids develop acidosis so readily on carbohydrate restriction or on high fat diets, and might in part account for the headaches that occur, especially those early in the morning before breakfast, a not uncommon symptom in cases of severe toxemia.

The absence of free hydrochloric acid in the gastric juice has been noted in several cases. This may account for some of the diarrhea that is sometimes an annoying symptom. The administration of dilute hydrochloric acid to these patients gave symptomatic relief, and in the few on whom this has been tried it has proved beneficial. Further studies are now being pursued on this subject by the gastro-enterologic department of this hospital.

Tremor of the tongue, fingers and toes is one of the most frequent physical findings, even in mild cases. It is not unusual, however, to see tremor in other conditions simulating hyperthyroidism—especially in functional neurosis and in cases of irritable hearts in which the differential diagnosis often has to be made by basal metabolism determination. The tremor of hyperthyroidism, however, particularly that of the fingers, if observed carefully, seems to be an uncoordinated tremor, each finger will be vibrating at a different phase and they are not synchronized. The best way to elicit this tremor is for the patient to spread the fingers widely apart and for the physician to support the hand with his thumb under the carpophalangeal joint of the middle finger. Tremor of the eyelids, arms, legs or whole body may occur, and the degree of tremor is not always commensurate with the toxicity. The body tremor can at times be choreiform. One case was so severe that it simulated Huntington's chorea.

Muscular weakness and fatigability usually are early signs. This for the most part is general, but not uncommonly affects one group of muscles more than another. One rather common group affected is the extensors of the thigh. The weakness of these muscles may be so extreme that the patient will volunteer the information that it is impossible to get up even very low steps, though he will be able to walk with ease on a level ground.

In well marked cases, evidence of vasomotor irritability is almost the rule. Flushing, dermatographia and sweating are evidences of a

⁴ Sanger, B. J., and Hun, E. G. Glucose Mobilization Rate in Hyperthyroidism, *Arch. Int. Med.* 30:297 (Sept.) 1922.

sympathetic stimulation, and can be accentuated, as can any other type of sympathetic irritability, by the subcutaneous injection of epinephrine. The Goetsch test, based on this response to epinephrine, has largely fallen into disuse as we see the same response in nonthyrotoxic cases of sympathetic irritability as in thyrotoxic cases.

A great deal of stress has been put on the value of the differential blood picture as a diagnostic aid. It was said that there was almost always present a distinct lymphocytosis. It was somewhat surprising, therefore, to discover that in the majority of these cases the differential picture was essentially normal. The total number of red blood cells, white blood cells and the hemoglobin content usually are normal in uncomplicated cases.

In the female the evidence of relation of the ovarian system to the disease is striking. It is not uncommon to have some type of menstrual disturbance associated with hyperthyroidism, most usually an irregularity of the menses or an amenorrhea. The common observation of the increase in size of the thyroid at puberty, during the menstrual period, or during some phase of pregnancy is another evidence. Pregnancy occurring in the course of treatment or in recently cured cases will frequently rekindle a thyrotoxicosis. In three of our cases this has occurred, but the recurrence was promptly relieved by further treatment.

In all cases of true exophthalmic goiter the basal metabolism is elevated above normal. Almost every symptom can be referred to the increased cellular metabolism. The thyroid hormone is a cell stimulant, hence the increase of total metabolism in all cases of hyperthyroidism. The basal metabolism therefore gives us the best index of the toxicity of the gland. The apparent derangement of carbohydrate metabolism is one of storage, not of utilization, that is, there is no fault with specific carbohydrate utilization. It is probably because of this failure to store carbohydrate that the fasting quotient in cases of exophthalmic goiter is somewhat lower than normal, being somewhere around 0.76.

A detailed case history of all patients included in this paper will not be given, as they all presented typical histories and physical findings of exophthalmic goiter. Only those, therefore, that for one reason or another seem of importance or point out some particular phase of the problem will be cited in brief.

Three cases with auricular fibrillation seem especially interesting. They do not include the whole number of cases with this complication, but in their essential features they epitomize the group.

REPORT OF CASES

CASE 1—E. R., a white traveling salesman, aged 35, married, entered the hospital, Feb. 17, 1920, complaining of cardiac palpitation, nervousness and shortness of breath. The family history was negative, except for the fact that one

sister was supposed to have had goiter. The previous history was essentially negative. The present illness dated back three years, when the patient had first noticed rapid heart action. He later developed tremor of the hands, excessive sweating, and dyspnea on exertion. Struma had been present for about one year. Some loss of weight had occurred early in the disease, but at the time of admission the patient had regained his normal weight. Tonsillitis also had occurred early in the disease, and the patient had had his tonsils removed. The shortness of breath recently had increased to such an extent that he sought hospital attention. Physical examination showed a well developed and well nourished young man weighing 63.6 Kg. The skin was moist and flushed. The patient appeared somewhat nervous, but was without frank exophthalmos, though the eyes were bright and somewhat staring. Joffroy and Moebius signs were present. The thyroid gland was diffusely enlarged, but no bruit or thrill could be made out. The heart was normal in size and position, its action was irregular in force and rhythm. The character of the heart sounds were suggestive of mitral stenosis, but no murmurs were definitely heard. There was a fine tremor of the fingers and toes. The blood pressure was 150 systolic, 80 diastolic. Physical examination was otherwise negative. The electrocardiogram showed auricular fibrillation, there was a marked pulse deficit. The basal metabolism on admission was 55 per cent above normal. The sugar tolerance test (100 Gm of glucose by mouth) gave an essentially normal response.

Under rest in bed and digitalis therapy the pulse deficit cleared up, although the heart action was still irregular in force and rhythm. October 23, the basal metabolism was 46 per cent above normal, with a respiratory quotient of 0.72.

The patient was discharged, March 6, much improved symptomatically, but with his heart still fibrillating and his basal metabolism still high. After leaving the hospital ambulatory treatment consisted in roentgen-ray therapy. June 23, after six treatments, the basal metabolism was still 51 per cent above normal, the pulse was 88, but still irregular, and digitalis was continued. August 16, after the eighth treatment, quite striking changes were manifest. He had felt a steady improvement, and finally there had been a disappearance of all his symptoms: shortness of breath, tremor, nervousness. He had been gaining in weight. On physical examination he now appeared calm, there was only a slight tremor, the struma persisted, although it was somewhat smaller, and the heart rate was regular and 84 to the minute. The basal metabolism had decreased to 8 per cent below normal. The electrocardiogram showed normal rhythm. Roentgen ray and digitalis were now discontinued and, September 25, the patient returned in excellent condition, with a metabolic rate of 6 per cent above normal. He is now back on the road as a traveling salesman, and doing his work without any difficulty. The heart action has remained entirely normal, and he has no signs and symptoms referable to his former disease.

CASE 2—D. S., a housewife, aged 26, entered the hospital for the first time, May 14, 1917, complaining of tremor of the fingers and excitability.

The family and personal histories were essentially negative. She dated the onset of the present illness from the birth of a child, Nov. 15, 1917. In December of that year she had an abscess of the breast, and soon after this she observed the tremor of her fingers and the increased irritability. Nine months later she discovered that her neck was getting larger and that she tired more easily. Three months before admission she began to have headaches, insomnia and sweating. She was conscious that she always felt warm and that she was losing weight. The weight on admission was 45.5 Kg.

Physical examination revealed a moist, warm skin, prominent eyes, with a distinct lid lag, large, infected tonsils, and marked tremor of the fingers. The thyroid was diffusely enlarged, the right lobe being somewhat larger than the left, elastic in consistency, with a systolic bruit and thrill over the gland. The heart was slightly enlarged, with a presystolic and systolic murmur at the apex and to the left side of the sternum. Otherwise the physical examination was essentially negative.

Under rest and high caloric diet she improved slowly, and was discharged, September 30, having gained 77 Kg. She was treated for a while by psychotherapy with good results, till June, 1919, when she was lost sight of. She came back to the hospital, March 30, 1921, with a history of fever and weakness of three weeks' duration, and generalized pain. Except for emaciation and fever, the physical examination was much the same as on the previous admission. The weight on admission was 40.9 Kg. It was decided that she had acute rheumatic fever, and she improved on salicylates. Her basal metabolism at this time was about 40 per cent above normal. During her stay she developed auricular fibrillation. Quinidine was given without any results.

May 16, radiotherapy was started and she received twenty-seven treatments between that time and June, 1923, with progressive improvement. She continued to fibrillate until some time after February, 1922. When seen in April of that year the pulse was regular and an electrocardiogram showed normal rhythm. She is now back to her normal status after a long, rather stormy course, entirely well, with a normal basal metabolism.

CASE 3—B S., a single white man, aged 34, a pressman, entered the hospital, May 8, 1922, complaining of nervousness and exophthalmos. The family history was negative, and the past history was negative except for the fact that he had had typhoid at 15.

The present illness dated back to the spring two years before, when the patient began to suffer from insomnia, and a tremor of the hands that interfered with his work. Finally he had to give up and go to the country because of what was termed a "nervous breakdown." He lost 9 Kg. and had profuse sweating and palpitation on the least exertion. In the fall he was able to go back to work much improved. Six months before admission friends had first noticed the prominence of his eyes, and he came into the hospital especially because of this. The chief findings were a moist, warm, flushed skin, extreme exophthalmos with all related eye signs, and gingivitis. There was marked carotid pulsation. The thyroid gland was not enlarged. He had a rapid, irregular pulse, and an electrocardiogram showed auricular fibrillation. The basal metabolism on admission was 55 per cent above normal.

On rest in bed, high caloric diet and two radiotherapy treatments this came down to 34 per cent above normal and the patient was discharged improved, to continue on ambulatory treatment. He had in all fourteen treatments. He had a subsequent admission to the hospital for quinidine therapy, but his fibrillation persisted. He now has no evidence of any myocardial insufficiency in spite of this, and is back on his job as a pressman, working from eight to twelve hours a day. He has had a normal basal metabolism, and has been free of all symptoms of hyperthyroidism since April, 1923.

In one case that occurred early in our series a hypothyroid state was produced, which has persisted in spite of thyroid medication. The following shows distinctly that the cumulative effect of radiation must be kept in mind.

CASE 4—F M., a single white man, aged 40, a mail clerk, came into the dispensary, July 16, 1921, complaining of goiter. The family and personal histories were negative except for the fact that the patient had had influenza in 1919. He dated the onset of the present illness from the attack of influenza, when he had noticed that his neck was getting larger. In the spring of 1920 he was at home for ten weeks because of nervousness, palpitation and shortness of breath. He was better after rest, and was able to go back to work. He came to the dispensary chiefly for nervousness and the goiter.

On physical examination he appeared nervous and excitable. There was a slight exophthalmos, with slightly positive eye signs. There was diffuse enlargement of the thyroid, the right lobe being somewhat larger than the left. A thrill

and bruit were present over both lobes. The heart was not enlarged. S_1 was loud and booming at the apex, followed by a low pitched systolic murmur. There was a presystolic gallop at the base. The reflexes were increased. The basal metabolism done July 16, 1921, was 38 per cent above normal, with a pulse of 100.

He had five radiotherapy treatments and, October 6, the basal metabolism was 2 per cent below normal, with a pulse of 68. All signs and symptoms of the thyrotoxicosis were gone except some shortness of breath on exertion. June 19, 1922, the basal metabolism went up to 15 per cent above normal, and two more treatments were given. The basal metabolism then went down to 25 per cent below normal, and it has remained approximately the same ever since.

He is back at work as a railroad mail clerk, but in spite of 4 grain (0.26 Gm.) doses a day of thyroid extract, his basal metabolism remains below normal.

Three patients were so toxic that they were not considered good surgical risks. They responded quite strikingly to roentgen-ray treatment, as their histories will demonstrate.

CASE 5—G. R., a woman, aged 28, a machine operator, entered the hospital, June 19, 1924, complaining of swelling of the neck of ten months' duration.

The family history was entirely negative, and the past history was negative except for the fact that she had had nose and throat infections for the last five years. She had had a tonsillectomy in 1919.

The onset of the present trouble dated back four years, when she first noticed nervousness, palpitation and loss of weight. She first noticed the swelling of the neck ten months before admission. Her own physician gave her roentgen-ray treatments (?) for a short while, with some benefit. Recently she was more nervous, and had a sinus infection.

On physical examination she was apprehensive and overactive. There was distinct exophthalmos. The thyroid was enlarged and rubbery in consistency, and bruit was present. The pulse rate was 110. There was marked tremor of the fingers. The admission basal metabolism was 60 per cent above normal. She was given rest and treated with sedatives without results, she was extremely restless and stimulated.

She improved on Lugol's solution and her basal metabolism came down, but at once rose again when Lugol's solution was omitted. This procedure was repeated with the same results. She was then started on radiotherapy, and straightway began to improve. After five treatments she had lost all her symptoms. She has been back at her rather strenuous work for almost a year now without any discomfort referable to her previous hyperthyroidism.

CASE 6—A. W., a man, aged 48, a newsdealer, entered the hospital, June 25, 1923, complaining of weakness, nervousness, swelling of the neck and loss of weight, extending over the previous three years. The family history was negative except for a strain of epilepsy, and the patient's own history was entirely negative. Three years before admission, following a shock, he began to have tremor of the hands and nervousness, and noticed that he tired easily. Soon after this his neck began to swell, and though his appetite was increased, as was his food intake, he lost weight. Recently he had palpitation with a definite increase of all his symptoms.

The physical examination revealed an apprehensive, anxious man, with moist, warm skin. There were patches of leukoderma over the face, hands and crural regions. There was a suggestive exophthalmos, with no lid lag, but a widening of the palpebral fissure. The tonsils were moderately hypertrophied. The thyroid was diffusely enlarged. The heart was enlarged and the pulse rapid, there was a fine tremor of the fingers. A basal metabolism done June 28, was 79 per cent above normal. Under rest and a high caloric diet he developed a severe diarrhea with further loss of weight. He was started on radiotherapy, and received three treatments before he left the hospital. He had a distinct anxiety neurosis during

his stay at the hospital, and finally left against advice, not much improved. Subsequent to his discharge he had two more treatments. The basal metabolism promptly fell to normal, where it has remained ever since. He has led an active life for the last two years, has been entirely relieved of all previous symptoms, and has gained 20 Kg. since the time he was first seen.

CASE 7—M. K., a housewife, aged 29, married, entered the hospital, May 9, 1923, complaining of goiter. Her father had died of heart trouble, and one aunt had a large goiter. The patient's own history was negative except for a pelvic operation seven months before admission. She had first noticed swelling of the neck while in Ireland two years before admission. Following the operation seven months before admission, she began to have hot flushes and nervousness. She soon developed nausea and vomiting, with resulting weakness and loss of weight. Subsequently nervousness became worse, and she noticed palpitations and shortness of breath. On physical examination she was seen to be a restless, agitated young woman, with moderate exophthalmos and positive eye signs. The thyroid gland was diffusely enlarged, soft, with evidence of increased vascularity. The heart was slightly enlarged and overactive, there was a soft systolic murmur at the apex, the rate was 105 and regular. There was a fine tremor of fingers, moist hands and hyperactive reflexes. The basal metabolism, May 22, 1923, was 102 per cent above normal. She had a distinct anxiety neurosis with a great deal of motor overactivity. With rest in bed, sedatives, and radiotherapy she began to improve but left the hospital against advice. She then was treated in the follow-up clinic and responded most satisfactorily to radiotherapy. In all she had sixteen treatments.

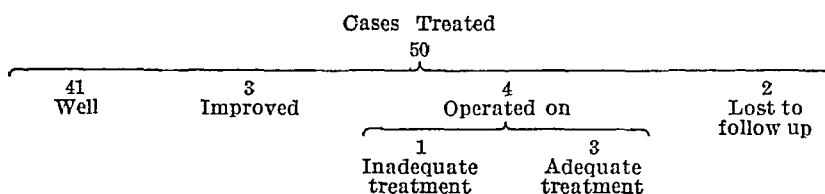
We now come logically to the treatment of these cases. It seems foolish to talk about remissions of the disease, or to say that it is self limited and let the matter of therapy rest there. Nor can we believe that masterful neglect will cure cases of exophthalmic goiter. Many of the cases in this series give long histories of thyrotoxicosis, with rest and all other types of therapy interspersed in their course. In spite of this most of them showed a progressive downward trend. It seems only reasonable in a disease that has such marked constitutional effects to treat it actively and reduce the general toxemia and increased metabolism as soon and as simply as possible, before any permanent organic change has occurred. It is not uncommon to see patients after treatment cured of their hyperthyroidism but having a residual myocarditis, or some other related organic change, which either partially or totally disqualifies them for an active, normal existence. One patient in this series was practically relieved of all signs and symptoms of exophthalmic goiter, but died because her myocardium was too badly damaged to develop any compensation.

Radiotherapy offers a simple form of treatment. It rarely causes the patient any discomfort at all. Only occasionally has there been any unpleasant reaction, characterized by malaise, nausea and vomiting, lasting at most from twenty-four to forty-eight hours. A great many of the cases in this series were treated as ambulatory patients, and went about their usual occupations, with advice to rest as much as possible and to take a high caloric diet. Only the patients that had severe myo-

cardial symptoms were advised to take a complete rest. From the case reports there can be little doubt of the efficacy of this form of therapy. One case that occurred early in our series proved conclusively that radiotherapy has a distinctly depressing action on the thyrotoxic gland. The history has already been cited in this paper as an example of the cumulative action of the roentgen ray (case 4). This is the only case in which treatment has produced a subthyroid state. Since this case has occurred we do not treat a secondary rise in the basal metabolism so promptly, as we feel that there is a distinct cumulative effect from the radiation, lasting sometimes several months.

The treatment has varied a little, with the several roentgenologists who have directed the radiotherapy, as to dosage and frequency of treatment, but when reduced to equivalents was essentially the same. The dosage used at present is 90 K V, 16 inch target skin distance, 5 milliamperes for twelve minutes, 3 mm aluminum filter.

Up to the present time we have treated fifty patients with radiotherapy. The results may be epitomized as follows:



There have been secondary rises in basal metabolism and concomitant reappearance of symptoms in four cases. All these have responded promptly to further radiotherapy, and have needed generally but one or two additional treatments.

The average number of treatments necessary for results has been ten. The greatest number of treatments given any one patient, with final recovery, was twenty-seven. The smallest number needed for the same end was three. There is no way of predicting beforehand how stubborn the cases are going to be to treatment. Not infrequently those with only a moderate rise in the basal metabolism are the most refractory.

The improvement in symptoms following radiotherapy usually is quite rapid. In most cases after three treatments, the patients feel distinctly better and appear less toxic. One of the most striking things noted is the early tendency to gain weight, and this often before there has been any fall at all in the basal metabolism. The extreme nervousness and sleeplessness soon disappear in the cases that are responding to treatment. In early cases palpitation and tachycardia are soon lost, but this symptom complex is more persistent in the cases of longer standing, as might naturally be expected. When there has been a real myocardial change this may persist for a long time after all symptoms

of the disease have disappeared, and the basal metabolism has reached normal. In occasional cases in which the damage has been great, it may continue permanently. Exophthalmos usually is one of the last things to disappear, though in occasional cases it has disappeared like magic after only a few treatments. Usually it persists in some degree for a long time after the basal metabolism has reached normal, and in cases in which it has been extreme may never recede much, although all the other symptoms will have gone and the patient be entirely over his hyperthyroidism. Tremor also tends to remain till the metabolism has struck a normal level, when it almost universally disappears.

The value of careful basal metabolism determination in the follow-up of these cases cannot be overestimated. It is the gage by which we regulate our treatment and reduce the activity of the gland to normal with the least possible chance of doing too little or too much. Our system has been to give a series of three treatments three weeks apart, followed by a basal metabolism three weeks after the last treatment, and subsequent series of treatments as indicated by the results of the test. Treatments must be given regularly every three weeks, till the basal metabolism is brought within the normal limits. Any irregularity militates against the best results. When the metabolism has reached normal, we follow the patient with basal metabolism determinations at monthly or two monthly intervals for the first four to six months, after that every six months from then on, but the patients are instructed to come in at any time between appointments if a return of their previous symptoms is noted. In this way any recurrence of a thyrotoxicosis is made out early, and can be depressed promptly by little additional radiotherapy. A long continued follow-up with frequent basal metabolism determinations is the only sound way of knowing the outcome of treated cases, and for this a personal follow-up is absolutely essential.

The important point in the clinical course of the cases included in this series is given in the accompanying tables. Some of the most recent cases have not had a very long follow-up, but are being included in this series, as an attempt to follow the histories for a number of years will be zealously made with a view toward increasing our knowledge of the ultimate results of therapy and the final prognosis of the roentgen ray as a therapeutic agent. It will be seen that radiotherapy does not cure all cases, just as operation does not, but in a final analysis the results are as good with much less inconvenience and economic disability to the patient. In a longer followed series it is my impression that the results will be better, as here we have an agent whose dosage and use can be closely controlled. It is not a haphazard matter of taking out just enough gland, not too much nor too little, a thing that comes only after a great deal of surgical experience, and even then does not lend itself to great accuracy. With radiotherapy controlled by frequent

Summary of Cases

Case	Date First Seen	Duration of Symptoms	Initial			Treatment	Date Last Seen	Last			Became Symptom Free with Normal Basal Metabolism	Duration of Follow Up	Remarks
			Weight, kg	Basal Metabolism, per Cent	Pulse			Weight, kg	Basal Metabolism, per Cent	Pulse			
1	1/29/20	1 yr	54.9	+31	104	3 roentgen ray, secondary rise, 3 roentgen ray	5/8/25	61.7	-2	68	10/11/21	5 yr 8 mo	Previous thyroidectomy, entirely well after radio therapy, following pregnancy, had slight secondary rise
2	2/7/20	3 yr	63.7	+55	106 (fibrillating)	8 roentgen ray	3/12/25	75.2	+6	84	8/16/20	5 yr 7 mo	Fibrillation, normal rhythm established when basal metabolism became normal
3	3/30/20	6 mo	59.7	+16	100	6 roentgen ray	1/4/21	63.8	+37			10 mo	Postoperative case, irregular treatment, slight improvement
4	4/6/20	1½ yr	50.2	+28	92	16 roentgen ray	11/7/21	62.8	+21	86		1 yr 7 mo	Slight improvement, moved away while still under treatment, subsequently operated on
5	6/12/20	3 yr	56.3	+47	116	13 roentgen ray	11/30/21	59.5	+23	100		1 yr 6 mo	Improved, lost to follow up while still under treatment
6	6/18/20	2 yr	47.2	+55	104	8 roentgen ray	9/19/23	57.7	-11	64	10/2/22	5 yr 3 mo	Entirely well
7	8/18/20	8 mo	51.6	+35	84	18 roentgen ray	7/22/25	56.4	+32	100	10/16/22	5 yr 1 mo	Improved somewhat, subsequently operated on
8	11/9/20	1½ yr	50.6	+56	120	13 roentgen ray	5/12/24	59.0	+13	92	2/28/23	4 yr 10 mo	Entirely well, slight secondary rise, exophthalmos persists
9	12/3/20	7 yr	48.8	+43	104	14 roentgen ray	4/24/25	57.9	+2	84	10/24/22	4 yr 9 mo	Entirely well
10	12/21/20	2 mo	55.2	+63	108	9 roentgen ray	10/31/21	60.5	+60	112		8 mo	Would not take treatments regularly, very slight improvement, died elsewhere
11	12/31/20	8 mo	39.0	+65	120	14 roentgen ray	7/25/21	36.5	+47	120		6 mo	Lost to follow up clinic before treatment was completed, improved
12	3/1/21	8 mo	57.7	+26	96	15 roentgen ray	3/14/25	55.0	±0	80	4/27/22	4 yr 6 mo	Entirely well, lost to follow up clinic 2 years after recovery
13	3/14/21	Indef	59.5	+37	82	13 roentgen ray	6/24/25	55.2	+2	76	4/4/24	4 yr 6 mo	Entirely well
14	4/1/21	2½ yr	49.0	+58	116 (Irregular)	10 roentgen ray	10/10/24	57.2	-5	68	2/18/22	4 yr 5 mo	Improved only slightly, subsequently operated on, now entirely well
15	4/8/21	8 mo	55.1	+99	144	24 roentgen ray	9/19/25	72.0	+10	68	9/26/24	1 yr 5 mo	Entirely well
16	4/9/21	1 yr	47.2	+35	100	24 roentgen ray	9/18/25	51.5	-8	64	1/31/23	4 yr 5 mo	Entirely well

17	4/16/21	3 wk.	49.0	+40	96	14 roentgen-ray	12/20/21	46.0	+37	104	8 mo	Well for 7 months, then developed carcinoma of stomach with rise in metabolism, died
18	4/23/21	Indef	53.2	+73	132	11 roentgen-ray	2/ 9/25	64.7	+ 6	84	4 yr 5 mo	Entirely well
19	5/ 4/21	3½ yr	39.3	+10	112 (irregular)	27 roentgen ray	2/18/25	52.9	± 0	72	4 yr 4 mo	Fibrillation, returned to normal after treatment, entirely well
20	7/16/21	2 yr	54.5	+38	100	7 roentgen ray	2/19/25	65.0	-13	56	4 yr 2 mo	Now has hypothyroidism, taking thyroid extract
21	9/ 6/21	3 yr	59.0	+105	102	11 roentgen ray	3/21/25	63.0	+15	80	4 yr	Entirely well
22	9/10/21	4 mo	52.0	+39	88	13 roentgen ray	4/23/25	54.5	+ 9	80	4 yr	Entirely well
23	9/12/21	7 mo	49.6	+48	138	14 roentgen ray	9/21/25	53.2	+ 6	84	4 yr	After first basal metabolism lost for 2 years, then treated, well
24	10/10/21	3 yr	54.2	+42	120	20 roentgen-ray	6/ 5/25	51.0	± 0	76	3 yr 11 mo	Entirely well
25	10/20/21	8 yr	60.8	+30	100	14 roentgen-ray	9/26/25	54.8	± 1	72	3 yr 11 mo	Entirely well
26	2/ 7/22	8 mo	50.0	+82	144	12 roentgen-ray	9/21/25	71.2	+12	92	3 yr 7 mo	Had hypertension, also had secondary rise, now normal, hypertension persists
27	3/ 3/22	4 yr	76.4	+23	100	7 roentgen ray	9/16/25	70.5	+18	100	3 yr 6 mo	Entirely well
28	3/14/22	7 mo	61.5	+50	128	11 roentgen-ray	9/19/25	66.8	- 2	80	3 yr 6 mo	Entirely well
29	5/20/22	6 mo	56.2	+55	92	14 roentgen ray (irregular)	6/15/25	72.1	-18	76 (irregular)	3 yr 4 mo	Entirely well, exophthalmos persists, still fibrillating
30	5/25/22	5 yr	48.4	+63	112	13 roentgen-ray	9/17/25	57.0	+ 8	72	3 yr 4 mo	Entirely well
31	6/ 9/22	1 yr	56.5	+23	116	6 roentgen-ray	9/23/25	65.0	- 3	80	3 yr 3 mo	Entirely well, has some exophthalmos
32	8/24/22	2 yr	50.7	+52	120	8 roentgen-ray	4/24/25	60.0	- 7	84	3 yr 1 mo	Entirely well
33	9/16/22	Indef	62.0	+35	106 (irregular)	10 roentgen-ray	6/30/25	63.0	+ 2	64 (irregular)	3 yr	Entirely well, still fibrillating, has large fibroid
34	9/22/22	4 yr	38.6	+48	100	3 roentgen ray	3/ 1/23	38.5	+24	100	4 mo	Was entirely well when last seen
35	10/10/22	1 yr	45.6	+62	100 (irregular)	6 roentgen-ray	2/ 3/23	45.5	+35	104 (irregular)		Improved greatly under treatment, died of severe myocarditis and decomposition
36	10/14/22	4 wk	50.0	+41	120	15 roentgen-ray	9/18/25	51.0	+11	76	2 yr 11 mo	Entirely well
37	1/16/23	4½ yr	61.2	+68	132	7 roentgen ray	4/ 3/25	64.6	+ 4	84	2 yr 8 mo	Entirely well
38	5/22/23	6 mo	41.1	+102	120	16 roentgen-ray	3/24/25	62.1	+ 4	68	2 yr 4 mo	Entirely well
39	6/11/23	6 mo	45.3	+44	100	6 roentgen ray	7/ 7/25	50.3	- 8	68	2 yr 3 mo	Entirely well
40	6/19/23	1 yr	40.8	+69	132	10 roentgen ray	10/ 2/25	45.0	-10	72	2 yr 3 mo	Entirely well
41	6/21/23	4 mo	45.5	+87	116	3 roentgen-ray	3/10/25	52.8	± 0	60	2 yr 3 mo	Entirely well
42	6/28/23	3 yr	56.8	+79	108	3 roentgen-ray	9/22/25	75.6	- 3	76	2 yr 3 mo	Entirely well
43	7/16/23	17 yr	65.3	+30	100	3 roentgen-ray	3/12/24	68.7	+ 9	84	2 yr 2 mo	Entirely well
44	8/ 6/23	2 mo	52.8	+52	128	14 roentgen ray	8/15/25	59.0	+19	124	2 yr 1 mo	Greatly improved, still has myocardial symptoms
45	8/26/23	Indef	47.2	+49	112	11 roentgen ray	1/10/25	66.4	- 2	68	2 yr 1 mo	Entirely well
46	10/31/23	6 mo	60.2	+43	112	7 roentgen-ray	9/12/25	63.1	+10	96	1 yr 11 mo	Well
47	11/23/23	4 mo	57.7	+38	92	5 roentgen ray	4/ 2/25	63.3	± 0	72	1 yr 10 mo	Well
48	12/13/24	2 wk	61.2	+34	114	6 roentgen ray	5/ 1/25	65.7	+ 4	88	1 yr 9 mo	Well
49	2/19/24	10 mo	57.5	+60	120	5 roentgen-ray	4/25/25	57.5	+ 4	64	1 yr 8 mo	Entirely well
50	6/18/24	2 yr	51.4	+59	96 (irregular)	4 roentgen-ray	12/16/24	54.9	+12	76	1 yr 3 mo	Well

basal metabolism determinations, we can depress the activity of the gland to within normal limits and by a watchful follow-up detect the first tendency to a secondary rise, and if this should occur, promptly institute further treatment

SUMMARY

Fifty patients with exophthalmic goiter have been carefully studied under roentgen-ray therapy. They were followed at frequent intervals during their course of treatment and subsequent to their recovery, with basal metabolism and clinical observations. Some have been followed for as long as five years. The great majority, 82 per cent, became entirely well and remained so. Of the remaining 18 per cent, 6 per cent were improved, 8 per cent were operated on, and 4 per cent were lost to the follow-up clinic during the last year, so that the ultimate result is doubtful.

On the whole, the roentgen ray offers a safe and satisfactory therapeutic procedure, with a high percentage of cures, in cases of exophthalmic goiter.

AN OCCUPATIONAL DISEASE AMONG ZINC WORKERS¹

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WITH THE COLLABORATION OF

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CINCINNATI

Any toxic properties of zinc resulting in chronic industrial disease are commonly denied. Recognition is given to an acute form of zinc poisoning under such designations as "spelter chills," "zinc fever," "brass founders' ague," "smelter shakes," etc. As early as 1888, Simon¹ in his description of this acute zinc poisoning records the absence of any chronic manifestations. Hayhurst² states, "The physician must get away from the idea of attempting to diagnose chronic zinc or brass poisoning, as there probably is no such condition." Later this statement is mitigated in discussing the possible chronic effects of brass poisoning² "In Chicago the fact that 85 per cent of 1,761 foundry workers (brass) were under 40 years of age, and only 1 per cent over 50 years, was explained by employers as due to 'slowing up' or beginning decrepitude, and by workmen, as gradual incapacitation from the inhalation of brass fumes and the strain of work. The constant intake and elimination of unusual amounts of zinc and copper from the system, along with the repetition of brass chills or the constantly forced immunity to the same, are enough to cause degenerative diseases." Seiffert³ advocates the recognition of a chronic poisoning among zinc smelters from zinc carbonate and zinc sulphate. The principal evidences of this condition are exhibited in gastro-intestinal lesions. Hayhurst,² in commenting on this work, fails to agree that this constitutes chronic zinc poisoning. "It would seem rather to be a local irritative reaction due to the zinc salts mentioned."

It is generally conceded that workers in zinc processes often present chronic industrial diseases. These conditions are usually blamed on antimony, arsenic or lead, which are found in these processes as impurities either in the zinc or in the substances used in conjunction with zinc,

¹ From the department of bacteriology and preventive medicine, University of Cincinnati College of Medicine, and the Industrial Health Conservancy Laboratories, Cincinnati

1 Simon, R. M. Remarks on Brassworkers' Diseases, Brit. M. J. 1887, 1888

2 Kober and Hayhurst. Industrial Health, Philadelphia, P. Blakiston's Son & Co., 1924, pp. 333, 342, 329, 330

3 Seiffert. Beteiligung von Blei und Zink am Zinkhüttensiechtum mit Bemerkungen über hygienische Massnahmen in den Zinkhütten, Öffentliche Gesundheitspflege, 1918, 3:44

such as sulphuric acid. The characteristics of these occupational diseases (lead, arsenic and antimony) are fairly well known. However, on close examination of workers in zinc (galvanizers) the manifestations of their diseases do not always convincingly coincide with these known characteristics.

Tradition has injected many trite statements into the literature of zinc toxicology, such as, "metallic zinc is per se nontoxic", "only caustic salts of zinc are harmful", "zinc is not stored in body tissues". Slowly these traditions are being broken down. Malloy and Parker⁴ have produced a nephritis in animals as the result of subcutaneous implantation of pure metallic zinc. Several workers⁵ have detected stored zinc in the liver, muscles and (or) other tissues, both in man and in the lower animals. The gastro-intestinal irritation, long attributed to the local action of swallowed zinc salts, has been demonstrated following their intravenous injection⁶.

It is the purpose of this article to assemble the available evidences supporting the occurrence of chronic zinc poisoning, and to correlate these evidences with the tentative findings from our own work in two zinc industries.

ACUTE ZINC POISONING "SPELTER CHILLS"

Although acute zinc poisoning is a well established disease entity, no satisfactory explanation exists as to the mechanism through which it is induced. Hayhurst² believes that a reaction akin to anaphylaxis is caused by the zinc fumes sealing the mucous membranes of the upper respiratory tract. Since zinc may be found in the urine and feces following an attack, others believe that the condition represents a direct systemic action of the zinc. Whatever the explanation may be, it is believed that zinc oxide alone is capable of producing zinc chills. In 1845 Blandet⁷ supplied an accurate description of this disease condition in connection with the founding of brass.

The physiochemical state of zinc oxide in the form of vapors recently derived from molten zinc is definitely unlike that of the zinc oxide powder used in paints, linoleum, rubber, etc. The toxicity of the latter form is regarded as of minor significance as compared with the quick and severe manifestations at times following the inhalation

4 Mallory, F. B., and Parker, Frederick, Jr. Experimental Intracapillary Glomerulonephritis, *Proc. Am. A. Path. & Bacteriol.*, 1925.

5 Ghigliotto, C. The Normal Existence of Zinc in the Human Organism, *Chem. Abstr.* **14** 1373 (May 10) 1920. Rost, E. Zinc and Copper, Regular Constituents of the Human Body, *Die Umschau*, 1920, **24** 201-202.

6 Schwartze, E. W., and Alsberg, C. L. Pharmacology of Cadmium and Zinc with Particular Reference to Emesis, *J. Pharmacol. & Exper. Therap.* **21** 1 (Feb.) 1923.

7 Blandet. Colique de cuivre, *Ann. d'hyg.* **33** 461, 1845.

of zinc fumes present around galvanizing, zinc smelting, brass founding, etc

The basis of this difference in physiologic effects is discussed in detail by Drinker⁸ Reference is made to Drinker's excellent article for a critical review of the literature of zinc oxide toxicology

Impurities (lead, arsenic, cadmium, antimony) need scarcely be considered as possible factors in the causation of zinc chills since the work in 1910 of Lehmann⁹ He was able to produce typical zinc chills from the burning of chemically pure zinc

Opportunities for acute zinc poisoning are much greater in founding alloys of zinc wherein the metals with which the zinc is alloyed have a higher melting point, as in the manufacture of brass. The zinc constituent has a melting point of 419.4 C, while copper melts at 1,083 C In a mixture of copper, 75 per cent, and zinc, 25 per cent, the melting point of the mass is about 920 C, which is the approximate boiling point of zinc Although a vapor tension of zinc exists at a much lower temperature than its boiling point, this higher temperature favors the production of a state of zinc oxide capable of inducing acute zinc poisoning

In galvanizing, acute zinc poisoning is rare under normal operating conditions although zinc fumes arise in abundance This is owing to the low temperature generating these zinc fumes, this being only about 468 C When, however, galvanizing pots are in need of repair, and the fire is drawn, it is sometimes necessary to take out the remnants of zinc through melting with oxyacetylene torches This higher temperature favors the ready occurrence of zinc chills

After exposure for a few hours to recently burned zinc oxide, the mucous membranes, eyes and bronchi have a feeling of dryness and of soreness This may lead to a "hacking cough," to a feeling of a "belt being around the chest" The workers become weak, may vomit or be nauseated, headaches are frequent The foregoing may take place at the foundry but more often is first noticed after leaving the work place The victim becomes chilly and goes through the usual characteristics of a malaria-like chill Nothing greatly aids in obtaining warmth This period of distinct chills may last for the short period of thirty minutes or may continue throughout the greater portion of the night (occasionally it occurs during the day time) During this stage and for some hours thereafter, there is an intense thirst not easily satisfied Hot drinks are acceptable, hot milk is often used Both objectively and subjectively the patient is severely ill At times the condition disappears by crisis asso-

8 Drinker, P Certain Aspects of the Problem of Zinc Toxicity, *J Indust Hyg* 4 177-197 (Aug) 1922

9 Lehmann *Arch f Hyg* 72 358-381, 1910

ciated with profuse perspiration and deep sleep. On awaking some patients are entirely recovered except for weakness and distaste for food. Others describe a continuous lassitude over a period of days, usually calling for catharsis.

New workers, and old workers who have been away, are more apt to be afflicted. Wet weather favors the occurrence of zinc chills. Hayhurst² states that about 75 per cent of workmen regularly employed develop an apparent tolerance.

There is no reason to believe that if there is a chronic form of zinc poisoning that this acute form is a forerunner or is necessarily related. In our cases of possible chronic zinc poisoning only one of the patients has given a history of antecedent zinc chills.

GENERAL TOXICOLOGY OF ZINC

Zinc may be found in various human tissues and excreta as a result of eating foods containing zinc. Shell-fish are known normally to contain zinc.¹⁰ Van Itallie,¹¹ in discussing the normal content of zinc, arsenic and copper in the human body, reports the finding of appreciable quantities in the liver of twenty-four subjects. Ghugliotto⁵ examined the organs of twenty-two persons dead of accidents. The zinc content (as zinc oxide) varied from 0.0015 to 0.0028 per cent of the viscera. Zinc was also found in the fetus.

Rost¹² has found among nonindustrial workers the presence of zinc in urine and feces. The average daily excretion in the urine ranges from 0.6 to 1.6 mg (as zinc oxide) and in the feces varied from 9 mg to as high as 39 mg. The source of the zinc is to be found in galvanized pipes, cooking vessels, cosmetics, etc. Salkowski¹³ tested plum marmalade made in a zinc lined vessel. A zinc content of 3.4 per cent was found, estimated as the sulphate. Peterson, Haines and Webster¹⁴ point out that milk, vinegar, soup and olive oil may be contaminated with zinc from storage in zinc containers. Some zinc is found in practically all foods. The zinc content in samples of beef, veal, pork and mutton ranged from 26 to 50 mg per kilogram, in beef liver a maximum of 83 mg per kilogram was found, in bread from 5 to 8 mg, in dried vegetables 6.13 mg and in cow's milk 3.9 mg.¹² Giaya¹⁵ examined eight human subjects ranging from the unborn to 70 years

10 Bodansky, Meyer. *Biochemical Studies on Marine Organisms*, II, The Occurrence of Zinc, *J Biol Chem* **44** 399-407 (Nov.) 1920.

11 Van Itallie. *Normal Zinc, Arsenic and Copper Content of the Human Body*, *Nederl Tijdschr v Geneesk* **63** 1709 (May 10) 1919.

12 Rost (Footnote 5, second reference).

13 Salkowski. *Zentralbl Biochem u Biophysiol* **19** 345, 1918.

14 Peterson, Haines and Webster. *Legal Medicine and Toxicology*, Ed 2, Philadelphia, W. B. Saunders Company, 1923.

15 Giaya. *Compt rend Acad d Sc* **170** 906, 1920.

Zinc was found in all. The amount increased in proportion to the age. His findings convinced him that zinc toxicity is lacking when stored zinc is less than 0.05 Gm per kilogram of viscera.

In man the zinc content in milligrams per kilogram of tissue was found by Rost¹² to be: liver, 52 to 146; musculature, 47 to 52; brain, 11. Zinc workers excrete zinc long after they discontinue work in zinc industries. Rost believes that zinc may be absorbed through the intestinal tract, stored in the liver and muscles, and excreted in the urine, feces and milk. Salant, Rieger and Treuthardt¹⁶ find that zinc is stored in considerable quantities in the liver.

From the foregoing it is obvious that the qualitative detection of zinc in human organs or excreta may be without significance. However, these data establish the storage of zinc in the human body, thus militating against the theory that zinc is harmless because it is not stored.

Mallory and Parker⁴ have recently reported nephritis in animals due to the action of metallic zinc implanted subcutaneously. Schwartze and Alsberg⁶ investigated zinc sulphate as an emetic. In the course of this work, intravenous injections of zinc sulphate brought about a gastric and intestinal inflammation. Salant,¹⁷ after feeding rats weighing from 150 to 200 Gm from 10 to 15 mg of zinc acetate daily for four months, observed no impairments with the possible exception of renal disturbance. Sacher¹⁸ reported that zinc fed rabbits developed albuminuria, renal congestion and gastric petechial hemorrhage. Brandl and Scherpe¹⁹ fed zinc to animals and on necropsy observed hemorrhage into the gastric mucosa, renal congestion and cloudy swelling. Salant and Wise²⁰ introduced small quantities of zinc (10 mg per kilogram of animal weight) directly into the circulation and noted as a result marked injury to the kidneys, nephritis and glycosuria leading to death in a few days.

Wherry²¹ injected zinc acetate intravenously in dilutions of 1:20,000 of rabbit body weight. No manifestations developed in this experiment until the third day when the animal was found dead. A dilution of 1:32,000 per body weight was nonfatal. A higher con-

16 Salant, W., Rieger, J. B., and Treuthardt, E. L. P. The Distribution and Elimination of Zinc and Tin in the Body, *J. Biol. Chem.* **34** 463 (May) 1918.

17 Salant, W. The Pharmacology of Heavy Metals, *J. Indust. Hyg.* **2** 72-78 (June) 1920.

18 Sacher, A. Zur Kenntniss der Wirkung der Zinksalze, *Arch. f. Pharmakol. Inst. zu Dorpat*, **9** 88, 1893.

19 Brandl and Scherpe. Ueber zinkhaltige Aepfelschnitte nebst Versuchen über die Wirkung des apfelsauren Zinks, *Arch. d. k. Gsndtsamte* **15** 185, 1899.

20 Salant, W., and Wise, L. E. The Production of Glycosuria by Zinc Salts, *J. Biol. Chem.* **34** 447 (May) 1918.

21 Wherry, W. B. Regarding four unpublished experiments, 1922. Personal communication to the authors.

centration than 1 20,000 caused immediate death, or death within a short time. In the one case in which death followed a 1 20,000 dilution, on postmortem marked edema of the lungs was observed, a sero-hemorrhagic exudate into the peritoneal cavity, marked nephritis and swollen, gray kidneys with petechial hemorrhage. The stomach was not examined.

Application of zinc as treatment for cancer, particularly of the uterus, has led to absorption and systemic poisoning.

A skin disease attributed to zinc oxide powders has been found among workers in that chemical by Turner²². McCord and Kilker²³ have described ulcers on the extremities of workers in a wood preservation plant wherein zinc chloride was used as a fungicide.

Witthaus²⁴ enumerates fifty-nine deaths from the effects of zinc chloride, and twenty-nine from zinc sulphate. In all of these, the zinc salt was taken in error, or for suicidal purposes or given for homicidal purposes. Both the immediate and the late results center about the corrosive or irritant action on the intestinal tract. The lethal dose is not known because of the emetic action of these salts leading regularly to loss of at least part of the substance. The smallest known quantity of the sulphate causing death was 15.5 Gm.

Blyth²⁵ records the developments in a patient who died fourteen weeks after taking a tablespoonful of "Burnett's fluid," an aqueous solution of zinc chloride.

There were at first violent vomiting and purging, but she suffered little pain, and in a day or two recovered sufficiently to move about the house, but the vomiting after food continued, everything being ejected about five minutes after swallowing. Before death she suffered from pneumonia. The stomach is seen to be much contracted—5 inches in length, it is ulcerated both near the pylorus and near the gullet, at the latter part there is a pouchlike portion of the mucous membrane of the stomach adherent to the spleen, which communicates by a perforation with an abscess formed and bounded by the stomach, diaphragm and spleen, it contained 3 ounces of dirty looking pus. At the pylorus, in the center, there is a second perforation, but extravasation of the contents is prevented by the adherent omentum and transverse colon.

In discussing sulphate of zinc Blyth states, "The infrequency of fatal results is due not to any inactivity of the salt but rather to its almost always being expelled by vomiting."

22 Turner, J. A. An Occupational Dermatoconiosis Among Zinc Oxide Workers, *Pub Health Rep* 36 2727 (Nov 4) 1921.

23 McCord, C. P., and Kilker, C. H. Zinc Chloride Poisoning, *J. A. M. A.* 76 442 (Feb 12) 1921.

24 Witthaus, R. A. *Manual of Toxicology*, New York, William Wood & Co., 1911.

25 Blyth, M. W., and Blyth, A. W. *Poisons Their Effects and Detection*, London, Charles Griffin & Co., Ltd., 1906, pp 690-692.

This review of the toxicology of zinc is not offered as a complete one. Sufficient is here included to convince that this metal has a greater toxicity than is commonly recognized by either zinc industrialists or physicians.

INDUSTRIES IN WHICH ZINC IS UTILIZED

We are listing below the major industries in which zinc in some form is found. This listing does not at all imply hazards to health in any degree or form. In some mentioned industries zinc poisoning is fairly common, in others, zinc poisoning is not known to have occurred, and in still others there are reasons to believe that zinc poisoning would not occur.

Processes involving the mining and smelting of zinc

Processes involving the manufacture of brass and other zinc alloys

Processes involving the manufacture of zinc salts and zinc oxid

The galvanizing industry and sherardizing

The rubber industry

The paint industry

The manufacture of oilcloths, linoleums, etc

The manufacture of galvanic battery plates

The manufacture of certain kinds of paper

The desilverization of lead

The manufacture of certain kinds of glass

The manufacture of certain dyes and mordants

INDUSTRIES IN WHICH ZINC IS UTILIZED

In two galvanizing plants in this locality we have studied workers and processes. In the first of these we have had a group of male workers under daily observation for three years. The number at work at any one time has not exceeded twenty, but on account of the high turnover the total number observed has been much higher. The men as a rule have been drinkers, have been users of tobacco to excess, have presented infected mouths, their eating habits have been bad, and their economic conditions have caused worry and stress. With a few exceptions, all workers are related by either blood or marriage. Most of the older men have been farmers and as a result present "weathered skins" and keratoses.

The work place is one room (45 by 45 feet) in which both pickling and galvanizing are carried out. The details of trade processes are recorded in another section. All work is done by hand. There are many openings in the roof and in the side walls. A large hood is in place above the zinc vat. Notwithstanding, fumes from the zinc vat and from the pickling tubs are visible. These tend to pervade the entire room and to mingle

During the last three years those workers who have been longest employed (from five to twenty-two years) have come to us for the medical care of divers gastro-intestinal complaints. All histories suggested gastric or duodenal ulcers or hyperchlorhydria. Complete examinations were not possible on account of the fear or ignorance of these workers. Although some workers have passed out of this factory we have been able to see in those who have remained an increasingly severe condition, until it became imperative to investigate the cause.

The second plant is much larger. The work is limited to the galvanizing of sheets of metal and all is done by machinery. The workers do not come so closely in touch with materials used. The type of employee is the same. In this plant our personal observations have been limited to conferences with the plant physician and chemists, casual conferences with suspected workers, perusal of medical records, limited direct study of processes, analyses of blood, urine, dusts, etc. In this second plant we found evidences of acute zinc poisoning from "overheated metal," and of the dermatitis described by Turner²² as caused by zinc oxid. We found the usual quantity of degenerative diseases, embracing divers cardio-renal and rheumatic conditions. We found, however, none of the gastro-intestinal conditions so common in Plant 1. The subsequent development of this material will supply a possible explanation of this difference.

TRADE PROCESSES INVOLVED IN THE PLANTS UNDER OUR OBSERVATION

In order that the presence of the substances potentially responsible for this occupational disease may be explained, the various steps in the galvanizing process are here detailed. "Galvanizing" is the term designating the coating of iron or steel with zinc. The first step is to prepare the material to be galvanized so as to present a clean metal surface, in order that it can "take" the coat of zinc. The cleansing of iron from adhering rust, scale or other foreign substances with acids is known as "pickling." There are several acids that may be used, sulphuric, hydrochloric, hydrofluoric. Sulphuric acid is the agent most commonly employed.

In Plant 1 the various tubs, buckets and cans to be galvanized are made from sheet iron. These sheet metal objects are placed in a large vat containing water and sulphuric acid. A gross rule of thumb governs the concentration and the temperature to be maintained. A solution of 7.5 per cent acid and a temperature of 150 F probably represent optimal conditions. The sulphuric acid in this weak solution is not freely volatile, but it is sprayed into the air by rising bubbles and carried away by the steam arising from the vat. In the pickling process large vol-

umes of hydrogen are evolved White²⁶ points out that as much as 1.05 cc of hydrogen may be set free from every square inch of non metal following pickling This liberated hydrogen is capable of combining with the sulphur present as an impurity in the sheet iron, and with the arsenic found as an impurity in zinc

After pickling the sheet non objects are sometimes immediately submerged in molten zinc, but at other times are rinsed in dilute hydrochloric acid solution at room temperature Some galvanizing plants allow for drying before submerging in molten zinc, others rinse in plain water, but in Plant 1 the object is submerged wet from the dilute acid

The zinc chamber is roughly 4 by 8 by 3 feet in depth Heating is obtained through the use of city gas, which is known to contain a small percentage of carbon monoxide A flue for oven fumes extends up above the level of the workers' heads, emptying into a larger hood placed over the entire zinc chamber The molten zinc is kept at a temperature of 468 C The surface of the molten zinc is divided into two parts by a partition On the surface of one part there is a superimposed layer of ammonium chloride that serves as a flux In addition to ammonium chloride used in this step, admixed zinc chloride is often used Mixed with the ammonium chloride are small quantities of "cereal middlings" to fluff it up From time to time during the day, there is placed into the molten zinc small bars of a commercial combination of metals called "silver metal" This serves as a brightener for the galvanized surface This "silver metal" contains aluminum and tin Several workers stand directly over the molten zinc These workers are engaged in submerging and lifting out articles to be galvanized The work is at a high temperature at all seasons The galvanized articles are allowed to drip free of molten metal and after a few minutes are removed for stripping of adhering particles and for storage

The foregoing processes for galvanizing hold true in a general way for all plants galvanizing small articles, cans, tubs and such utensils In the second plant, the galvanizing is limited to flat sheets of metal All sheets are of the same size and essentially all processes are carried out by machinery Instead of recounting in detail the trade processes involved, only items different from those described above will be mentioned In the latter plant, after pickling by machine dipping, all sheet metal is redipped in lime water to neutralize the acid Although vapors arise visibly from both of these kinds of vats, there is no obvious mingling of fumes until far above the breathing level of workers These vats are some distance away from the molten zinc vats in which

26 White, G. A. A Metallurgical Study of the Steel Base as Related to Galvanizing, Buffalo, Matthews-Northrup Works, 1918

no intermingling of fumes is noticeable at low levels. Prior to submersion in molten zinc a dipping is made into ordinary water. It is believable, therefore, that no gross distillation of zinc chloride or zinc sulphate takes place at this point. Other differences of lesser import have been noted, such as the use of tallow as the fluffing agent instead of middlings, and the blowing of sulphur dioxide fumes over the surface of the molten zinc. In this second plant no "silver metal" is used.

It has already been noted that in Plant 2 no cases of the occupational disease under study have arisen. It is believable from analyses made that the same impurities of crude materials are common to each plant. The type of workmen is similar although no "old timers" are found in Plant 2, owing to past labor difficulties. The following differences in the processes involved may serve to explain the difference in health conditions.

Plant No 1

- 1 The workroom is small with low ceiling and visible mingling of fumes
- 2 The pickling and galvanizing vats are placed relatively close together, favoring the admixture of fumes
- 3 All work is done by hand with men in close proximity to chemicals employed
- 4 Pickled objects, wet with acid, are submerged directly in molten zinc through flux of ammonium chloride
- 5 The majority of the workers have been employed in excess of six years
- 6 "Silver metal" is used

Plant No 2

- 1 The workroom is large, with the ceiling 65 feet above ground level, with mingling of fumes only at high levels
- 2 Vats for pickling and galvanizing are at a greater distance
- 3 All work is done by machinery, with the men kept at considerable distance
- 4 Pickled objects are submerged in lime water to neutralize the acid and later into tap water, prior to submerging in molten zinc through flux of ammonium chloride
- 5 Practically all the workers have been employed less than six years
- 6 "Silver metal" is not used

ANALYSES OF MATERIALS AND DUSTS ²⁷

Since, in our opinion, exposure over long periods of time is necessary to develop the condition being studied, not a great deal of information is to be gained from analyses of materials used at this immediate time. Materials in use in the course of twenty years have been obtained from different sources, made by different processes, without doubt containing varying quantities of impurities. Analyses have been made, however, on some materials. In other instances acceptable recorded analyses have been utilized. It is our purpose in recording these analyses to indicate the general character of impurities.

The sheet iron, later to be galvanized, presented the following impurities: carbon, manganese, sulphur and phosphorus. The quantity of these impurities varies. According to White,²⁶ the percentage is approximately: carbon, 0.13 per cent, manganese, 0.38 per cent, sulphur, 0.04 per cent, phosphorus, 0.065 per cent.

²⁷ A portion of the analytic investigation was conducted by the Langdon-Meyer Laboratories, Cincinnati.

Analysis of the substance (Klean-rite) which is placed into the sulphuric acid to facilitate pickling indicated 98 per cent commercial sodium chloride and 2 per cent organic material

The ammonium chloride tested 98 per cent pure ammonium chloride

Analyses of spelter by Ingalls²⁸ are accepted by us as representing the average spelter in use. One analysis is here cited, showing the impurities mixed in with the zinc

Lead	Iron	Cadmium	Arsenic	Antimony	Copper	Bismuth	Silicon Oxide	Sulphur	Carbon
0 0701%	0 7173%		0 0603%	0 0249%	0 1123%		0 0346%	0 0035%	0 1775%

The sulphuric acid in current use tested 76.9 per cent. Traces of lead were found. Negligible traces of unrelated impurities were detected.

Analyses of dust settlings taken from ledges near the galvanizing vat in Plant 1 were made on several occasions of which two are cited

Analysis 1—Qualitative

A sample of the dust settling above the galvanizing pot and representing probably the condensable portion of the fumes to which the operator is subject shows a trace of antimony, much zinc, iron, sulphides, sulphates and chlorides, as well as some material insoluble in strong boiling acids

Analysis 2—Limited Quantitative Analysis

	Per Cent
Sulphur as sulphates (SO ₃)	14.20
Iron and aluminum oxides	8.92
Zinc as Zn	35.00
Ammonia as NH ₃	6.25
Chlorides, Cl ₂	18.50
Sulphur as sulphide	0.08
Calcium	traces
Arsenic	doubtful traces

In Plant 2, a specimen of ledge dust was taken at a level of about 45 feet above the heads of the workers. The analysis exhibited constituents as follows

	Per Cent
Sulphur as sulphates (SO ₃)	17.29
Iron and aluminum oxides	6.65
Zinc as Zn	45.5
Ammonia as NH ₃	10.35
Chlorides as Cl ₂	13.36
Hydrogen sulphide	0.06
Lead	traces
Tin	traces
Water soluble material	55.32
Antimony	0
Arsenic	0

A qualitative analysis of "spelter dross" revealed zinc, iron and aluminum, together with doubtful traces of arsenic.

In the galvanizing room of Plant 1, zinc oxide comes into contact with sulphuric acid in the presence of moisture. The combination of these two substances leading to the formation of zinc sulphate is regarded by us as a certainty. Similarly, the combination of zinc oxide with hydrochloric acid leads to the formation of zinc chloride. One of

²⁸ Ingalls, W. R. Metallurgy of Zinc and Cadmium, Eng. & Mining J., London, 1903

the consulting chemists aiding us on this point sought to determine the precise amount of these zinc salts through methods based on the measurement of the total amount of molecular material available for combination. The figures indicate the presence of zinc sulphate in the ledge dusts of Plant 1 to the extent of 15 per cent, and zinc sulphide to the extent of 0.72 per cent. Other chemists accept with certainty the presence of zinc sulphate, zinc chloride and zinc sulphide, but recommend the avoidance of fixing any precise percentage. Thorpe²⁹ attests to the formation of zinc chloride under the conditions mentioned.

The ammonium chloride, used as a flux in galvanizing, is gradually lost during the process, and fresh additions have to be made as required. This loss is doubtless due in part to volatilization of the salt itself, but also to a reaction which takes place whereby zinc chloride is formed and ammonia set free.

From these analyses, recognition must be given to a number of potentially harmful substances, such as hydrogen sulphide, arseniureted hydrogen, arsenic, mineral acids, ammonia, ammonium chloride, lead, antimony, cadmium, aluminum, zinc, zinc oxide and zinc salts.

A faithful consideration of these potential hazards leads us to the attachment of greater significance to the zinc salts accidentally formed as described in the foregoing. We are influenced in this tentative decision by the results of earlier cited animal experiments, wherein chemically pure zinc or zinc salts have been utilized. It is impracticable to incorporate here all the consideration given to the other potential intoxicants. The general trend of our consideration of these other substances is indicated in the items now cited. Concurrent with this series of galvanizing cases we have studied a group of lead cases from a storage battery plant. The manifestations have been markedly dissimilar in these groups, except in the anemia and constipation present. Using the method of McCord, Minster and Rehm for the detection of basophilic material, large amounts of this substance have been found in all but one of our lead cases, while in the series of galvanizers only one of those tested has exhibited large amounts of basophilic material. From the consideration of cadmium as a possible cause, it is to be pointed out that this metal is so volatile that it is almost entirely eliminated in zinc smelting. If this were the producing agent, the disease under study might be expected to be more prevalent among zinc smelters. Arsenic, of course, must be considered since this material is present as "traces" in our analyses. In chronic arsenic poisoning the absence of arsenic pigmentation of the skin is unusual. Other characteristics, such as "arsenic pock," paralysis of muscles and peripheral neuritis are fairly constant. If our cases were attributable to arsenic surely some

²⁹ Thorpe, T. E. *Dictionary of Applied Chemistry* 5, New York, Longmanns Green & Co., 1913.

percentage of our patients would present these outstanding characteristics of arsenic poisoning. In a similar manner the other potentially harmful substances have been studied and tentatively ruled out as producers of the entire symptom complex. We are, however, receptive to the idea that where so many potential hazards exist "mixed poisoning" may occur.

REPORT OF CASES

CASE 1—A man, aged 37, who had been a galvanizer for about twenty years, Feb 5, 1924, consulted us because of "stomach trouble," which had been present for several months. He had had one severe attack of pain in the epigastric region. For several weeks he had had a burning pain in the epigastrium, beginning two or three hours after meals. This pain was relieved by food. There was occasional vomiting of "coffee grounds" vomitus. He had marked constipation and frequent severe headaches, but no knowledge of blood in stools. A limited examination at that time established tenderness in the epigastrium. The patient declined treatment. June 7, 1924, the patient consulted us on account of a severe epigastric pain. Treatment was again refused. May 2, 1925, the patient submitted to a limited examination and treatment.

The history taken and the examination made at that time revealed that the patient had been essentially well until the present illness. For a long time he had had palpitation of the heart and continuous constipation. He had had a gonorrheal infection two or three times during his life. He had frequent toothaches in various teeth.

In the past he had taken whisky three times a day, beer three times a day, and coffee three times a day. He now drinks moonshine, and at times becomes thoroughly drunk.

He had begun work as a newsboy at the age of 10 years. He was a sandpaperer of heels in a shoe factory at the age of 15 years. At about 17 years he began his present employment, at first as a porter, but he soon "went on kettle," where he remained until the present time.

His best weight was 135 pounds (61.2 Kg) with an average of 130 pounds (59 Kg). His present weight was 130 pounds. His height was 5 feet 8 inches (172.7 cm). He was a fairly well developed, poorly nourished adult of rather poor intelligence.

The skin showed a marked pallor, the lips were of poor color, and the skin was scarred by metal burns. Numerous metal burns appeared around the face and neck. No eruptions, small pigments, moles or nevi were noted, and no marked myotatic irritability.

The eyes reacted to light and distance, and the extra-ocular movements were normal. Astigmatism was present. An ophthalmoscopic examination was negative. The disk outlines were sharp. There were no hemorrhages. The arteries were not contracted.

The teeth were in poor condition, there were several bad roots and slight pyorrhea but no lead line. The tongue protruded in the midline without a tremor. The tonsils and pharynx were negative.

The inguinal glands were palpable, but the rest of the glands were negative.

The chest was slightly flat. Expansion was symmetrical and fairly equal on both sides. There was retraction at both apexes, greater on the right.

On percussion the lungs showed hyperresonance throughout, with hyperresonance over the heart area, the base posteriorly five fingers below the lower border of scapula. Breath sounds were increased over the entire chest. No râles or friction rubs were heard.

Relative cardiac dulness was 3.5 by 10 cm and retrosternal dulness 6.5 cm. The first sound was snappy at the apex. At the base a soft systolic murmur was heard over both areas, which was not transmitted up. There was a suggestion of sinus

arrhythmia of the respiratory type The cardiac rate was 100 The systolic blood pressure was 132, the diastolic 92 The temperature was 97.2

The abdomen was below the chest level The liver edge was not felt There was distinct epigastric tenderness, which was distinctly localized Apparently a contracted wall of the colon could be felt (rolled under the finger)

The reflexes were slightly increased There was no Babinski reflex The biceps reflex was double plus

Blood examination, May 9, 1925, revealed hemoglobin, 80 per cent, red blood cells, 3,200,000, white blood cells, 5,800, polymorphonuclear leukocytes, 62 per cent, small lymphocytes, 35 per cent, large lymphocytes, 2 per cent, and transitionals, 1 per cent The Wassermann reaction was negative Urinalysis, May 14, showed a volume of urine of 350 cc said by the patient to be a twenty-four hour output Zinc (as Zn) was 0.35 Gm per liter³⁰ June 9, the volume of urine was 970 cc in twenty-four hours, it was acid to litmus and negative for bile The sulphates were 1.89 Gm per liter, chlorides (Cl_2), 1.42 Gm per liter, iron and aluminum oxides, 0.525 Gm per liter There were slight traces of tin Zinc (as Zn) was 0.189 Gm per liter There were slight traces of albumin, it was negative for sugar and for blood The patient was not working at time of either urinalysis

Roentgen-ray examination showed evidence of two ulcers, one duodenal and one pyloric

CASE 2—A man, aged 40, at present an inspector of galvanized products, from 1903 to 1910 was a galvanizer, from 1910 to 1918 worked in the lead industry, from 1918 to 1923 was a galvanizer, and from 1923 to 1925 an inspector He stopped galvanizing two years before examination because of an ulcer of the stomach, diagnosed and treated by his family physician June 2, 1925, the patient gave a history of being on a rigid diet for irregular periods, the chief foods being milk and eggs Continuous tenderness was present over the epigastric region with pain radiating to the right and to the left There were tarry stools at frequent intervals, with occasional fresh blood to the extent of 3 or 4 spoonfuls in a stool

On examination the patient was found to be somewhat undernourished He was pale, and there was a grayish brown tinge to the exposed portions of the skin There were a few scars from galvanizing on the exposed parts of the skin The patient exhibited the usual characteristics of unhealed, persistent ulcer

Blood examination, June 6, 1925, revealed hemoglobin, 80 per cent, red blood cells, 3,470,000, white blood cells, 5,200, polymorphonuclears, 69 per cent, large lymphocytes, 4 per cent, small lymphocytes, 26 per cent, and myelocytes, 1 per cent

Roentgen-ray examination did not establish ulcer

After conference with the patient's family physician a diagnosis of ulcer was accepted

CASE 3—A man, aged 32, a galvanizer for twelve years distributed over a period of seventeen years, had worked at five different galvanizing plants, always doing hand work

Five years before examination, the present difficulty started with belching of gas and sour stomach The condition had become slowly worse since that time Three years before he had attacks at about six week intervals of severe abdominal pain with vomiting and inability to eat most foods Between attacks, a dull pain was continuously present At times he was unable to work, and he was continuously dizzy

Vomiting had been a constant feature The vomitus was described as being at times "coal black", at other times greenish, containing clots of blood Fre-

³⁰ Quantitative urinalyses for zinc were carried out by the wet incineration method after evaporation of the urine to a small volume After separation of other metals, zinc was precipitated by hydrogen sulphide The zinc was weighed as $\text{Zn P}_2\text{O}_5$ and calculated as metal zinc This method is subject to possible error The analyses were made by F. J. Andress, University of Cincinnati

quently, there had been periods when "tarry" stools were regular. The patient was in the hospital three years before on account of "stomach trouble."

At the present time the patient complained of pain in the epigastrium and also just inside the right iliac crest. During the last month there had been three attacks of severe pain with vomiting. At times he was able to eat any food except "sours." When the pain was severe, practically all food was vomited except chilled milk. Baking soda at times caused vomiting. At times the eating of food stopped pain, at others the pain was increased by food, and at still others relief came about two hours after eating.

The examinations made were without significance except in the following respects. Moderate abdominal tenderness was present around the umbilicus, in the right iliac fossa and beneath the xiphoid. No rigidity and no masses were noted. Roentgen-ray examination established some inconclusive evidence of postpyloric ulcer although clinically the condition was regarded as gastric ulceration.

Blood examination revealed hemoglobin, 90 per cent, red blood cells, 3,690,000, white blood cells, 6,750, polymorphonuclears, 68 per cent, small lymphocytes, 29 per cent, large lymphocytes, 3 per cent, and basophilic aggregation test, 2 plus.

Urinalysis indicated normal urine without any evidence of impaired renal function, a qualitative test for zinc was positive.

CASE 4—A man, aged 58, worked as a galvanizer for sixteen years, doing all the jobs connected with galvanizing. He quit work as a galvanizer five years before examination because of "stomach trouble." There was no record in the case of alcoholism or excessive use of tobacco.

Previous to doing galvanizing work the patient was exceptionally well. This continued for eight years after he began galvanizing. The patient first suffered from nausea, distention and gastritis. Two years after the onset the condition became severe, necessitating absence from work for considerable periods. There was pain over the entire abdomen radiating upward, over the lower ribs and in both axillary lines. The pain was sufficiently severe to prevent sleeping. He vomited almost daily. Baking soda gave relief but foods afforded relief only at times. "Tarry" stools were not observed. There was no diarrhea and no constipation. Headache over the top and front of the head was fairly constant. During the years of abdominal disturbance the patient also suffered from a dermatitis which he attributed to the chemicals employed.

After six years of attempting to work with this abdominal condition, the patient quit and became practically an invalid for two or three years. During the last three years the patient had been doing farm work, which had been his occupation prior to his becoming a galvanizer.

At the present time he vomits a great deal, at least on an average of three days a week. Occasionally he has severe attacks of pain and vomiting, lasting two or three weeks. Baking soda gives some relief. The vomitus is sour, but not of "coffee grounds" type, it contains food. The patient eats practically all foods but states that many do not agree with him.

CASE 5—A man, aged 29, a galvanizer for about seven years, was said to have more severe trouble than any other worker, but refused all cooperation. Other members of the family and fellow workmen were consulted. The condition had begun about one year before the investigation as "stomach trouble." He had lost considerable time owing to the condition, was unable to eat, and had several severe attacks. He was now on a meat-free diet. No direct history was taken by us, no examination was made, and no diagnosis.

CASE 6—A colored man, aged 29, who was employed in a third plant never inspected by us under unknown work conditions, had worked at galvanizing for seven years. He had done pickling as well as all "jobs around the kettle." He was first seen, Nov. 13, 1924, on account of zinc chills, probably associated with lead poisoning, he recovered.

June 1, 1925, he discontinued work and became a truck driver, leaving the galvanizing work because of increasing impaired health. During the previous six

months he had had five severe attacks of abdominal pain, which came on at night and which were relieved by baking soda or by drawing up the limbs tight across the abdomen. He was unable to eat many kinds of food, particularly acid foods and meat. In addition to severe attacks of pain, there had been a fairly continuous dull pain in the abdomen, and there were intermittent severer pains in the abdomen between meals. The patient was constipated at times. This increased the severity of the abdominal pain. No tarry stools and no vomiting were noted, but there was some belching of gas and distention of the abdomen at intervals.

CASE 7—A man, aged 51, a galvanizer for eighteen years with an aggregate loss of one year during the eighteen, two years before examination developed "stomach trouble." He was on a strict diet for nine months. The pain was located over the epigastrium and in the back of the left side. There was a low grade ache in the abdomen, with patient having occasional severe attacks. He was markedly constipated and the abdominal pain was worse when he was constipated. The pain was more noticeable between meals, eating was known to relieve the pain. He felt no pain at night, provided he ate supper. At the present time he was on a strict diet.

The routine examination of the patient was without significance except in the following respects. The patient, who was large framed and muscular, presented a pale skin and pale mucous membranes, exposed portions of the skin were of brownish tinge with keratoses. There was distinct tenderness in the abdomen, well localized over the duodenal region.

Blood examination revealed hemoglobin, 80 per cent, white blood cells, 5,600, red blood cells, 3,960,000, polymorphonuclears, 61 per cent, small lymphocytes, 34 per cent, large lymphocytes, 3.5 per cent, transitionals, 1 per cent, myelocytes, 0.5 per cent, and basophilic aggregation test, 6 plus.

Examination of the urine revealed total volume 870 cc, it was acid to litmus and negative for bile. Sulphates (SO_4) were 1.162 Gm per liter, chlorides (Cl), 4.43 Gm per liter, iron and aluminum oxides, 0.176 Gm per liter, and zinc as Zn, 0.31 Gm per liter. There were traces of albumin, it was negative for sugar and blood, there were traces of lead.

Roentgen-ray examination established bilateral fibrosis of the lungs and marked gastric hyperperistalsis. The stomach and the duodenum were of regular contour.

In this case we are convinced that lead was a contributory factor. Examination of the blood showed an excess of basophilic material. Traces of lead were found in the urine, and clinically there was a record of long standing rheumatism of a character suggesting lead arthritis.

CASE 8—A man, aged 46, a galvanizer for about twelve years, had worked "off and on" for galvanizer employers during a period of twenty-two years. He did night work. The present condition began about one year before examination. This was first a nausea which was severe enough to cause loss of time from work. Pain in the abdomen became sharp in character, and was more severe before meals, particularly before the evening meal, following a day of sleep. Food at once relieved pain. Constipation aggravated the condition.

At the present time there were no remissions except when he was away from work for two or three days, when the condition became less severe. There was marked distention of the abdomen at frequent intervals but no belching of gas. The patient had noted "coal colored" stools and dark colored urine.

CASE 9—A man, aged 38, for fourteen years had been a galvanizer with his present employer, for seven years he had done dipping. The general history was without significance except that he had been a heavy drinker of beer. Years before the examination he had had malaria. Since he had been galvanizing he had suffered from eye strain, headaches, and blurring associated with headaches. His best weight was 160 pounds (72.6 Kg), with an average of 155 pounds (70.3 Kg), his present weight was 154 pounds (69.9 Kg).

About a year and a half before examination "stomach trouble" developed. This was not well defined until about eight months before, when he began to feel a dull ache in the pit of the stomach. This pain would appear two or three hours after eating and would continue until the next meal was taken or until some food was eaten. The eating of food always relieved the pain. This "ache" in the stomach was usually accompanied by the belching of gas and sour eructations, occasionally by nausea. The patient gave no history of having vomited, nor had he noticed anything unusual about his stools. The abdominal pain mentioned varied from what the patient called a "dull ache" or "hungry feeling" to a fairly sharp pain, which never was so severe as to double him up. Occasionally, a dizziness occurred, especially on reclining or tipping the head backward. In the morning there was a foul taste in the mouth although the appetite for breakfast was fair. At no time had the eating of food caused the patient any distress. There were no diarrhea, no constipation and no recognized intestinal pain. At no time were there remissions represented by weeks or months.

CASE 10—A man, aged 66, a galvanizer for eighteen years, now doing other work or no work, was in a state of mental confusion due to alcohol.

This patient gave a typical ulcer history with pain so severe that many nights he lay doubled across a board fence. He had severe attacks at least once a month for many years. The patient was of the opinion that the condition started prior to the beginning of galvanizing work. A history was obtained in a local hospital suggestive of ulcer. No great significance was attached to the patient's statements.

CASE 11—A man, aged 38, a galvanizer for about eight years, with some irregularity in his work, two years before examination developed distention of the abdomen, noticed particularly in the morning before breakfast. Later this was associated with nausea and later with abdominal pain. The pain was more severe when the patient was constipated. He had "heartburn" and had lost some weight. The pain was localized in the right iliac region and over the epigastrium. There was tenderness on pressure. Alkalis gave immediate relief. An ulcer diet had led to marked improvement.

Details of the physical examination made are omitted except the following laboratory findings.

A blood count, May 9, 1925, revealed hemoglobin, 70 per cent, red blood cells, 2,770,000, and white blood cells, 7,050. An after-treatment blood count, June 6, revealed hemoglobin, 75 per cent, red blood cells, 3,440,000, white blood cells, 8,000, polymorphonuclears, 67 per cent, small lymphocytes, 28 per cent, large lymphocytes, 4 per cent, and myelocytes, 1 per cent.

Urinalysis revealed total volume, 850 cc, it was acid to litmus and negative for bile. Sulphates (SO_4) were 2.86 Gm per liter, chlorides (Cl_2), 4.75 Gm per liter, iron and aluminum oxides, 0.656 Gm per liter. There were traces (distinct) of zinc as Zn. It was negative for albumin and sugar, and gave doubtful traces of blood.

A roentgen-ray examination was without significance.

Case 12 is cited as an example of a group coming under our observation in which the patient was not so severely afflicted as to be classed with the foregoing.

CASE 12—A man, aged 34, had been an irregular galvanizer since 1908, his present employment began five months before examination, he worked on the night shift. After working three and one-half months the patient developed what he termed indigestion. He noted that various foods, particularly fruits, onions and cucumbers, caused abdominal distress. He had distention of the abdomen, with severe cramps. The pain was located around the umbilicus.

The pain at the present time was essentially constant. Foods made the pain worse. Constipation increased the pain. Relief was obtained by expelling gas.

At times he belched particles of food, and said that he belched up materials that put his "teeth on edge"

Case 12 is representative of a group of employees at work for shorter periods, from six months to five years, including one man who "off and on" had worked during twelve years. Only two men who had worked in excess of eight years were free of abdominal disease.

The high incidence of gastro-intestinal disease in this group under observation is much in excess of what is true for this type of person in industry in general. In Plant 1, of more than 200 workers in departments other than galvanizing, only one gastric or duodenal ulcer has been detected in three years.

We are well aware that in our examinations much helpful information has not been obtained. The type of worker has almost entirely precluded such tests as gastric analyses. Notwithstanding the absence of these desirable diagnostic aids, we are of the opinion that several of these workers have gastric or duodenal ulcers, certainly gastric or gastro-intestinal inflammation to a severe degree.

SUMMARY

In a small galvanizing plant, we have detected widespread gastro-intestinal conditions, varying from gastro-enteritis, in the younger workers, to well established gastric and duodenal ulcers among workers employed for a long time. Twelve out of fifteen workers employed seven years or longer have presented severe gastro-intestinal lesions.

In a second plant, in which all employees are new at this work (less than six years) and in which the general work conditions are better and exposure to trade process fumes is much less, no cases of this gastro-intestinal disease have been found.

We have shown the accidental formation of zinc sulphate and zinc chloride at levels and under conditions that involve exposure on the part of the workers in Plant 1.

In all workers whose urine has been tested, zinc has been found in quantities in excess of the accidental urine content from food, galvanized iron pipes, etc.

These patients have not presented the characteristics of other occupational disease hazards attending galvanizing.

We have sought to stress the occurrence of multiple hazards in the galvanizing industry. On this account we feel unwarranted in drawing any precise conclusions as to the etiologic factor in these cases. Although we attach significance to zinc as a causative agent, we accept various other substances as possible contributing factors. We also believe that the unhygienic conditions of the work place, together with

the physical type of worker, favor the occurrence of the conditions we have described

A close resemblance is seen between our observations of lesions among zinc workers and the findings in the literature referred to in which study has followed the administration of single, chemically pure substances. Our concept that zinc is capable of producing chronic systemic poisoning is aided (*a*) by the work of Mallory and Parker in obtaining kidney lesions from pure metallic zinc implanted subcutaneously, thus disproving the often repeated statement that metallic zinc is nonpoisonous, (*b*) by the work of several authors establishing stored zinc in appreciable quantities in various organs and tissues and in excreta of zinc workers, long after the discontinuance of zinc work; (*c*) by the creation of alimentary tract lesions by pure zinc salts administered intravenously and by mouth.

A long period of time expressed in years (from five to twenty) appears necessary for the production of the lesions described.

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THE BLOOD IN SMALLPOX DURING A RECENT EPIDEMIC

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HISTORICAL REVIEW

Biouardel is generally referred to as the first investigator who made studies of the blood in smallpox. In 1874 he published his observations on the behavior of the leukocytes in this disease and emphasized the presence of a leukocytosis "during the febrile remission between the period of eruption and of suppuration. He found them diminished during suppuration, an increase at this time or during desiccation signifying to him secondary pyogenic infection" ¹

Corroboration of these findings and additional observations, particularly the studies of the morphologic changes of the leukocytes and the differential count, were made by a number of men, notably, Pick (1894), Rogers (1900), Courmont and Montagard (1900), Weil (1901), Ferguson (1902), Perkins and Pay (1903), Magiath, Brinkerhoff and Bancroft (1904), and others. Kammerer (1910) and Erlenmeyer (1913) and, more recently, Pantasis (1924) reviewed the literature extensively and reported the analysis of their own findings. Schilling, during an epidemic of moderate severity in eastern Galicia during the war, and Hoffman, during an epidemic of mild cases in Havana in 1921, made similar studies.

There is an essential agreement among these observers as to the findings of major import in the blood in smallpox. These may be briefly summarized as follows:

There is, as a rule, a leukocytosis in all forms of smallpox and the degree of leukocytosis seems to be in direct proportion to the severity of the disease.

The uncomplicated discrete form may show little variation in the total leukocyte count throughout the course of the disease.

Occasionally, severe forms may show persistent leukopenia.

Hemorrhagic and purpuric cases usually show a persistent hyperleukocytosis.

There is a relative decrease in the neutrophilic leukocytes.

The mononuclear cells are definitely increased both relatively and absolutely.

Pathologic forms, such as the so-called "stimulation" or "irritation" forms, plasma cells, atypical lymphocytes, myelocytes, metamyelocytes and Arnett's young leukocytes are frequently found.

* From the pathologic laboratory of the Minneapolis General Hospital.

1 Magrath, G. B., Brinkerhoff, W. R., and Bancroft, I. R. The Leukocyte Reaction in Variola, *J. M. Res.* 6: 247, 1904.

The erythrocyte count and the percentage of hemoglobin are little affected except in severe pustular or protracted cases

Normablasts, polychromatophilia and anisocytosis are found in severe cases, and certain structural changes of leukocytes, such as the vacuolization and bluish discoloration of the cytoplasm and the condensation and fragmentation of the nucleus, also may be present in hemorrhagic cases

There is, however, no consistent agreement among the writers who attempt to correlate various total leukocyte and differential counts with the days of the disease

Relative frequency of certain cells, such as myelocytes, large mononuclear leukocytes and eosinophils at various stages of the disease also is in dispute

As to the practical value of the blood findings in the early diagnosis and prognosis of smallpox, opinions also differ. Many seem at least

TABLE 1—*Smallpox Patients Admitted to the General Hospital from March 1, 1924, to Feb. 28, 1925, Together with Figures for the Entire City of Minneapolis, the State Outside Minneapolis, and the Entire State*

	Cases	Percentage	Deaths	Percentage	Percentage of Total
Discrete pustular (mild)	191	39.8	10	5.2	2.1
Confluent pustular (severe and fatal)	110	22.9	55	50.0	11.5
Hemorrhagic pustular (severe and fatal)	131	27.3	106	80.9	22.1
Purpuric (fatal)	48	10.0	48	100.0	10.0
Total	480	100.0	219	44.0	
Percentage of all the city cases (1,276)		37.6		66.0	
Entire city	1,276	40.4	332	26.0	14.7
State (outside Minneapolis)	1,892	59.6	105	5.5	3.3
Entire state	3,168		437	13.8	

skeptical, while others (Weil, Courmont and Montagard, Erlenmeyer and Hoffman), consider them of practical importance. Few, if any, however, would seem to venture a definite diagnostic or prognostic significance in given findings without some clinical data.

It is to be noted also that the majority of the writers base their conclusions on the studies of a comparatively small series of cases (Pick, forty-two cases, Rogers, thirty-six cases, Courmont and Montagard, twenty-nine cases, Weil, twenty-four cases, Schilling, twenty cases, Pantasis, twenty cases). Their findings and conclusions would therefore seem of value, mainly, so far as they confirm the observations of other investigators.

ANALYSIS OF 250 EXAMINATIONS

An analysis of the results obtained from the examinations of the blood in approximately 200 cases of smallpox, representing all forms and stages of the disease during the recent epidemic in Minneapolis (Table 1) confirms in the main, the findings of the men just summarized. There are, however, certain additional findings of definite

value which may further serve as an aid in the diagnosis and prognosis of this disease

I may state here, parenthetically, that the difference between the blood findings of all the frank pustular forms and those of the purpuric form² is so strikingly constant that it seems necessary to record them separately in the following presentation

THE PLATELETS (TABLE 2, FIG 1)

Simon³ mentions the behavior of the platelets in smallpox in these words, "There is a great diminution of platelets during the febrile period and a material increase during the pustular stage" It is generally known that, in smallpox as in pneumonia, measles and certain

TABLE 2—Findings in Various Types of Smallpox

Stage*	Cases	Platelets			Total Leukocytes			Polymorphonuclears			Temperatures		
		High est	Low est	Aver- age	High- est	Low est	Aver- age	High est, per Cent	Low est, per Cent	Aver- age, per Cent	High est, De- grees	Low est, De- grees	Aver- age De- grees
Mild Pustular Form													
1	3	103 500	85 000	91,100	19 000	3 000	10 000	79	60	71	102.4	100.0	101.2
2	12	90 000	10 000	49 000	9,700	3,100	5,833	79	28	40	103.8	98	99.9
3	9	65,000	15 000	36,100	26,000	5,500	13,200	76	39	56.4	101.8	98.8	99.9
4	7	185,000	12 000	74,950	28,000	15,900	20 923	69	57	61.4	102.0	97.6	100.5
5	19	300,000	100,000	174 250	33,000	7,550	14,630	62	17	47	101.2	96.8	98.4
Severe and Fatal Pustular Forms													
1	6	75 000	35 000	51,660	21,000	7 700	13,700	88	75	83	103.8	99.4	101.8
2	16	75,000	8 000	31,368	31 340	8 000	13,024	89	75	82	106	102.2	103.5
3	19	62,000	6 500	25 450	33,000	6 000	14,700	93	53	66.7	103.8	99.4	102.4
4	9	160 000	45,000	98,818	31,500	13,500	17,950	70	54	62.7	103.6	97.0	100.4
5	15	350,000	115,000	184,630	37,800	11,500	22,636	84	41	70	104.2	97	100.5
Primary type†		Purpuric Forms											
1	13	72,000	11,000	36,300	37,000	4,400	21,600	73	10	39	103.2	98.2	100.3
2	9	65 000	15,500	32,750	52,000	11,000	26,336	57	6	28	100.4	97.2	99.8
Secondary type†													
1	8	35 000	8 000	23 150	31 340	9 000	14 500	88	52	76	103.6	99.6	102.6
2	8	62,500	7,500	23,750	21,500	11,500	16,070	79	38	64	105	99.4	102.3
3	7	20,000	5 000	13,500	30,600	4,600	15,431	73	8	40.6	102.3	98	99

* 1, preeruptive, 2, maculopapular, 3, vesicular, 4, pustular, 5, desiccation

† 1, first two days, 2, second three days, 3, last three days

other infectious diseases, there is a low platelet count at the onset. Beyond this fact, no further studies appear to have been undertaken by investigators with reference to the various forms of smallpox.

In the initial period of the mild form of pustular smallpox, an average platelet count is 91,100 per cubic millimeter (highest, 103,500, lowest, 85,000). This is followed by an average of 49,000 per cubic millimeter (highest, 90,000, lowest, 10,000) in the maculopapular period and of 36,100 per cubic millimeter (highest, 65,000, lowest, 15,000) in the vesicular stage. From this point it shows a steady rise through the pustular stage, when an average count is 74,950 per cubic

2 Ikeda, Kano. The Blood in Purpuric Smallpox with a Clinical Review of Forty-Eight Cases, J. A. M. A. 84:1807 (June 13) 1924.

3 Simon, C. E. Clinical Diagnosis, Ed. 9, Philadelphia, Lea & Febiger, 1916, p. 827.

millimeter (highest, 185,000, lowest, 12,000), into the desiccation period, with an average of 174,250 per cubic millimeter (highest, 300,000, lowest, 100,000). Practically the same course is followed in the severe and fatal pustular forms. The initial period is 51,660 per cubic millimeter (highest, 75,000, lowest, 35,000), the maculopapular period, 31,368 per cubic millimeter (highest, 75,000, lowest, 8,000), the vesicular stage, 25,450 per cubic millimeter (highest, 62,000, lowest, 6,500), the pustular stage, 98,818 per cubic millimeter (highest, 160,000, lowest, 45,000), and the desiccation period, 184,630 per cubic millimeter (highest, 350,000, lowest, 115,000).

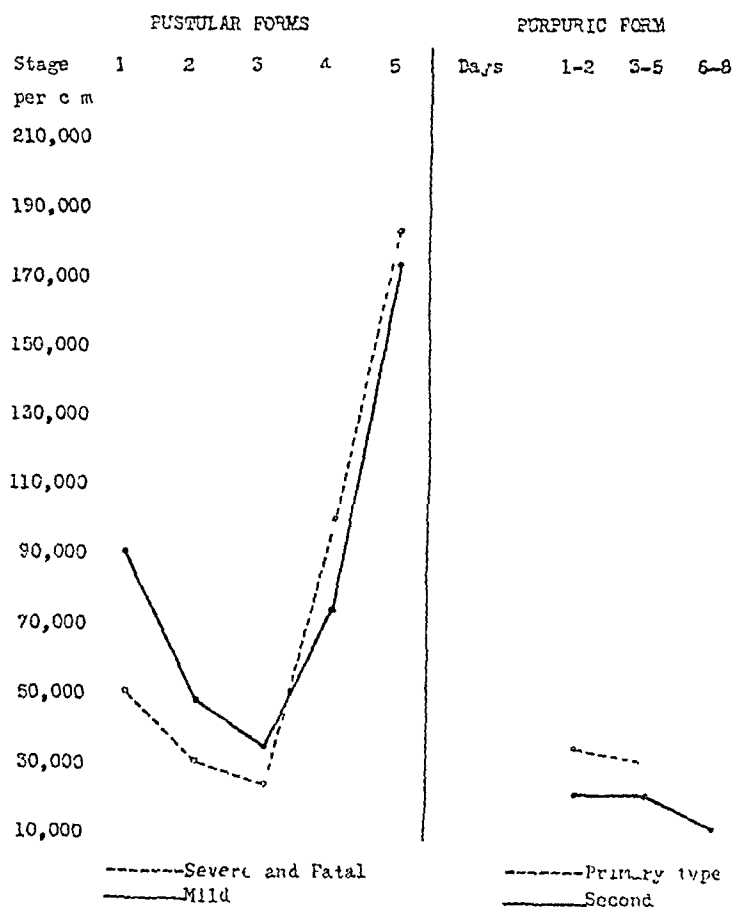


Fig 1—Platelet curve in various stages of the disease (Table 2)

In the purpuric form, there is a consistent fall until its termination. The appearance of the modified pocks in the secondary type does not in any way indicate a rise, as in the pustular forms. In the primary type, which shows no visible cutaneous lesions except the deep erythema, petechiae and ecchymoses, an average count is 36,300 per cubic millimeter (highest, 72,000, lowest, 11,000) during the first two days after the development of the initial erythema, and 32,750 per cubic millimeter (highest, 65,000, lowest, 15,500) during the next three days. In the secondary type which runs somewhat a prolonged course and which shows more or less extensive atypical vesiculopustular lesions,

an average count is 23,150 per cubic millimeter (highest, 35,000, lowest, 8,000) during the first two days after the initial rash, 23,750 per cubic millimeter (highest 62,500, lowest, 7,500) during the following three days, and 13,500 per cubic millimeter (highest, 20,000, lowest, 5,000) during the last three days

The rôle thus played by the platelet count in the differentiation of the purpuric form from the pustular forms of smallpox, and incidentally from eruptive and purpuric diseases, becomes at once of the utmost importance

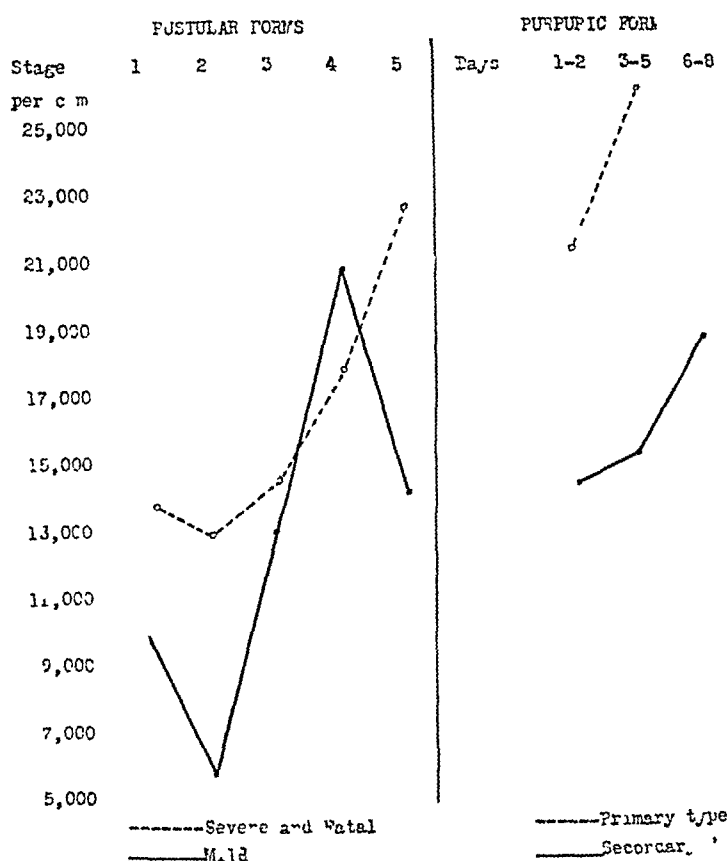


Fig 2—Total leukocyte curve in various stages of the disease (Table 2)

THE TOTAL LEUKOCYTE COUNTS (TABLE 2 AND FIG 2)

Magrath and his co-workers, using the data published by Pick, Courmont and Montagard, Weil and Ferguson, comprised a composite curve obtained from the average of 479 leukocyte determinations in seventy cases of uncomplicated variola vera. The curve thus obtained gives the following formula: relative or absolute hypoleukocytosis during onset and febrile remission, hyperleukocytosis during formative evolution of eruption, relative hypoleukocytosis at height of pustulation and hyperleukocytosis during desiccation. These seventy cases must undoubtedly include the mild as well as the severe and fatal forms of pustular smallpox. The average value thus obtained, therefore, would

not be a reliable index to a particular form that may come under observation

A leukocytosis (a high leukocyte count) is present, as a rule, during the initial period. In the mild form, an average count of 10,000 per cubic millimeter (highest, 19,000, lowest, 3,000) is obtained. There is, then, a definite decline to an average of 5,883 per cubic millimeter (highest, 9,700, lowest, 3,100) during the maculopapular period which is immediately followed by a sharp rise to an average of 13,200 (highest, 26,000, lowest, 5,500) in the vesicular stage. The highest average is reached in the pustular stage when it is 20,923 per cubic millimeter (highest, 28,000, lowest, 15,900). A decline to an average of 14,630 per cubic millimeter (highest, 33,000, lowest, 7,550) occurs in the desiccation period.

In the severe and fatal forms, an initial leukocytosis averages 13,700 per cubic millimeter (highest, 21,000, lowest, 7,700). It is maintained throughout the course of the disease, an average count being 13,024 per cubic millimeter (highest, 31,340, lowest, 8,000) in the maculopapular period, 14,700 (highest, 33,000, lowest, 6,000) in the vesicular stage, and 17,900 (highest, 31,500, lowest, 13,500) in the pustular stage, reaching its maximum during the period of desiccation, when an average of 22,636 (highest, 37,800, lowest, 11,500) is obtained.

In the purpuric form, likewise, an initial leukocytosis which averages 21,600 per cubic millimeter (highest, 37,000, lowest, 4,400) in the primary type and 14,500 (highest, 31,340, lowest, 9,000) in the secondary type, is maintained throughout the course of the disease. In the majority of cases, a terminal rise is noted, the primary type showing 26,336 (highest, 56,200, lowest, 11,000) during the third, fourth and fifth days after the initial erythema, and the secondary type, 15,431 (highest, 30,600, lowest, 4,600) during the sixth, seventh and eighth days. A leukopenia may be present in this form of smallpox (two cases) as in other severe forms of smallpox.

THE POLYMORPHONUCLEARS (TABLE 2 AND FIG. 3)

The polymorphonuclear neutrophil percentage shows a slight but consistent downward curve through various stages of the disease, regardless of its form or severity. It would seem safe to assert that the higher the polymorphonuclear percentage at the onset or during the initial period, the more grave the prognosis of the subsequent course.

In the mild form, an initial average of 71 per cent (highest, 79, lowest, 60) is followed by a definite drop to 40 per cent (highest, 79, lowest, 28) in the maculopapular stages. There is then a rise to 56.4 per cent and 61.4 per cent, respectively, in the vesicular and pustular stages (vesicular stage, highest, 76, lowest, 39, pustular stage, highest, 69, lowest, 57). This is again followed by a definite fall to 47 per cent (highest, 62, lowest, 17) in the desiccation period.

In the severe and fatal forms, a definitely high average of 83 per cent (highest, 88, lowest, 75) is noted in the initial stage. This is maintained in the subsequent period at 82 per cent (highest, 89, lowest, 75). There is, then, a definite decline during the vesicular stage with an average of 66.7 per cent (highest, 93, lowest, 53) which continues into the period of suppuration with an average of 62.7 per cent (highest, 70, lowest, 54). During the desiccation period an average is 70 per cent (highest, 84, lowest, 41).

In the purpuric form, a rapid drop of the polymorphonuclear neutrophil leukocytes with a continued high total count is consistently present.

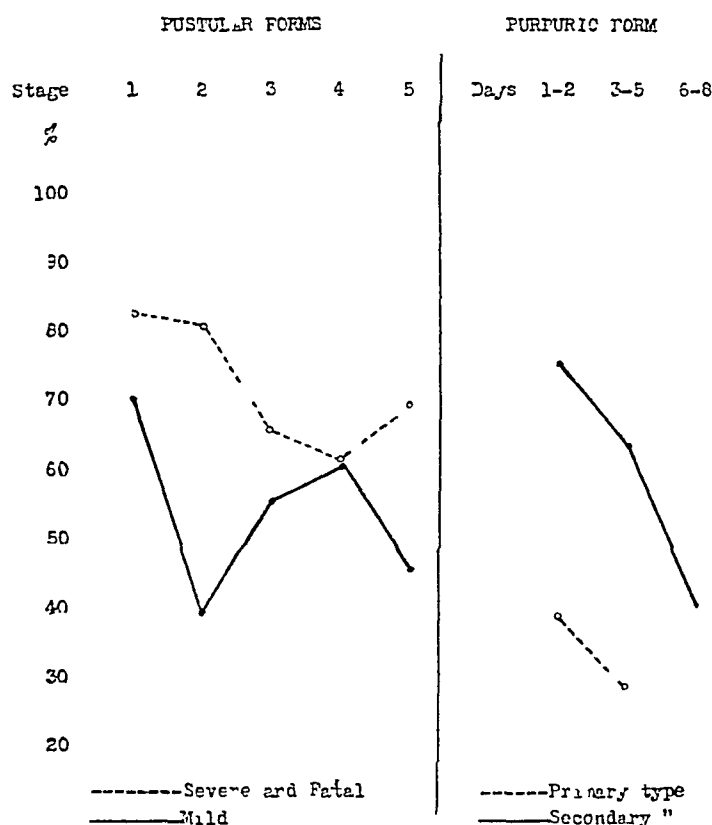


Fig 3—Polymorphonuclear percentage curve in various stages of the disease (Table 2)

In the primary type, an average during the first two days is 39 per cent (highest, 73, lowest, 10). During the subsequent three days, it is 28 per cent (highest, 57, lowest, 6). In the secondary type, an average during the first two days is 76 per cent (highest, 88, lowest, 52), during the next three, 64 per cent (highest, 79, lowest, 38), and during the last three days, 40.6 per cent (highest, 73, lowest, 8).

The rapid decrease and probably the ultimate disappearance of the polymorphonuclear leukocytes from the blood is effected by the disintegration of these cells by the toxin in the circulating blood together with the suppression of the leukocytopoiesis, and by the stimulation of the lymphocytogenic activity.

RELATION OF TEMPERATURE TO TOTAL LEUKOCYTES AND THE POLY-MORPHONUCLEAR NEUTROPHILS (TABLE 2 AND FIG 4)

Perhaps it would be of interest to dwell briefly on the relation of the temperature to the leukocyte and the differential counts at this time

In the mild form the temperature is seldom above 102 F at any period. It registers the highest average of 101.2 F during the initial period. In the severe and fatal forms the temperature runs considerably higher, often registering 103 and 104. The highest average is reached during the maculopapular period when it is 103.5, with the maximum of 106 and the minimum of 102.2. In the primary type of the purpuric form the temperature is rarely over 101, the highest average being 100.3 during the initial period. In the secondary type of the purpuric form it is 102.6 during the first three days. The total leuko-

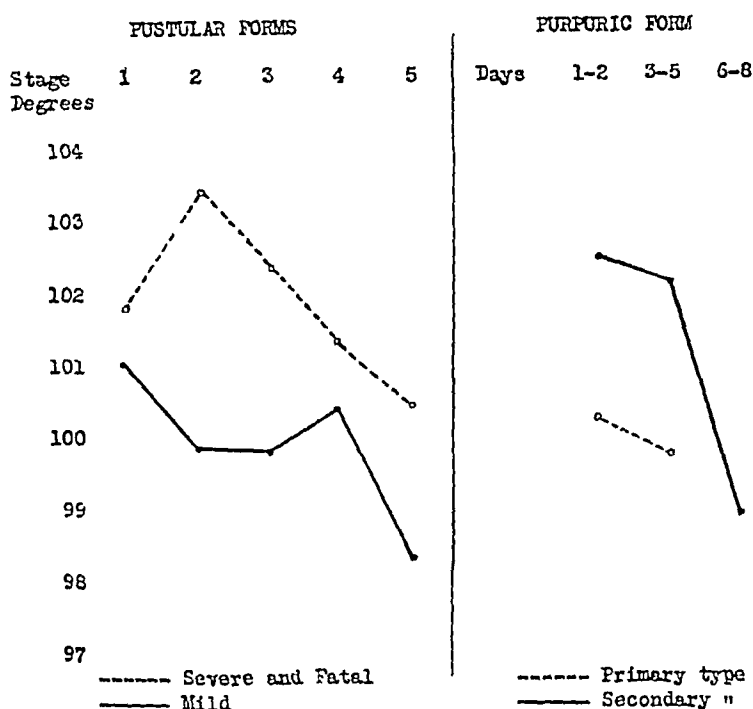


Fig 4—Temperature curve in various stages of the disease (Table 2)

cytes show their greatest increase during the later period of the disease, thus showing an entirely diametrical course, while the polymorphonuclear percentage shows its greatest value with the height of the temperature.

It is concluded from these observations that the polymorphonuclear percentage, like the temperature, indicates an immediate reaction of the patient to the infection while the total leukocyte count registers the response of the host to the accumulated insult by that infection.

It is further noted that the temperature in the primary type of the purpuric form is seldom greatly raised. This is probably explained by the presence of an element of shock which must necessarily accompany the diffuse hemorrhages as well as by the overwhelming power of the invading virus, the same as in any other fulminating infection.

THE ERYTHROCYTES

The number of erythrocytes is not appreciably affected in uncomplicated pustular cases. A moderate secondary anemia may develop with the pustulation. The severity of anemia is in direct proportion to the intensity and the extent of the skin lesions, to the amount of toxin absorbed, especially during the pustular stage and to the duration of the disease. It is further influenced by the presence of secondarily invading micro-organisms. Severe protracted cases may show a hemoglobin as low as 25 per cent, and an erythrocyte count of 1,500,000 per cubic millimeter or even less.

In the purpuric form, no appreciable quantitative anemia may be noted. This is particularly true in the primary type in which the course is exceedingly short and abrupt. In the secondary type, as in the severe pustular forms, a high degree of secondary anemia is, as a rule, present.

MORPHOLOGIC CHANGES

The erythrocytes show practically no morphologic or qualitative changes in the ordinary uncomplicated pustular form of smallpox. A secondary anemia, in varying degrees, is present in severe and protracted cases and in those with extensive secondary pyogenic infection, which in the majority of cases is caused by hemolytic streptococci. Low hemoglobin and erythrocyte counts, with a proportionate anisocytosis, polychromatophilia and occasional normoblasts, are the usual findings which persist well into the period of convalescence.

In the purpuric form, the constant presence of an increasing number of pathologic normoblasts, basophilic stippling and polychromatophilia, with a well sustained erythrocyte count and hemoglobin value, is a most striking finding. These regenerative changes of the erythrocytes are encountered even before the clinical evidences of purpura is discovered.

Such forms as plasma cells and "imitation" or "stimulation" forms are constantly found even in the mild form of smallpox. No special significance is attached to their presence. The so-called atypical forms of lymphocytes, which are seldom found in the normal circulating blood, are frequently met with, while the slightly immature forms are also encountered occasionally in severe cases. In the purpuric form, a high percentage of these lymphocytic cells may become a source of added confusion. A leukemia or an acute benign lymphadenosis may naturally be considered as a possibility on the blood smear alone, especially in the presence of a constant high leukocyte count as well as clinical signs of an acute infection. Early cells of the stem cell type and, as a rule, their immediate derivatives are not found.

Such structural changes of the leukocytes as are frequently present in severe sepsis or toxemia are found as a matter of routine. Their frequency depends on the severity of the disease. Even the mild cases

usually show an appreciable degree of these changes. Constantly found are the vacuoles, heavy azure granules, faint neutrophilic granules, clumps of basophilic chromatin in the cytoplasm, and the unilobular and unsegmented nucleus.

Myelocytes and metamyelocytes are often found even in the blood of the milder form. Their number is seldom more than 5 per cent of the total leukocytes, even in the more severe cases. Leukoblastic cells are also met with occasionally. The number of these cells serves in a measure as an index to the response of the bone marrow to the toxemia and therefore to the severity of the disease.

In the blood of the purpuric form certain specific changes are found in the mature leukocytes, namely, a condensation of the nucleus into darker staining homogenous rounded segments which gradually separate into individual nuclear bodies surrounded by more or less residual cytoplasm (Fig 5). These retrogressive changes are not in any way similar to those due to the disintegration of the leukocytes in the septic blood, or to the faulty technic in making smears. It is easily demonstrated that these fragmentary bodies are of a leukocytic origin by a careful study of the nuclear bodies and the remaining cytoplasm in a properly stained smear. It seems reasonable to assume that they are not of the bone marrow origin but rather formed in the circulating blood or within the diseased tissue by the direct insult of the specific toxin virus on the mature leukocytes. In other words, they represent a true degenerative phenomenon of leukocytes which occurs in certain infectious or toxic processes, the nature of which is not fully understood. Their close resemblance to the normoblasts and to the micro-lymphocytes should not confuse a careful observer.

At the beginning of this investigation, I was struck with the constant early presence of these fragmentary bodies in the blood of purpuric smallpox. I was soon convinced that similar bodies were consistently absent in the blood of all pustular forms of smallpox. It was therefore provisionally assumed that they were found only in the purpuric form of this disease. This was justified by the subsequent results. Every one of the forty or more cases of purpuric smallpox examined showed these bodies in the blood smears, while none of the more than 200 cases of pustular smallpox showed them at any stage of the disease.

These bodies were discovered during the routine examination of the blood smears and were given their just significance long before I began to consult the literature. Several investigators found the similar bodies in the blood of "hemorrhagic" smallpox and described them. None of them, however, gave their presence a significance which it deserved.

Further search for these bodies was conducted in the blood of exanthematous, septic and toxic disease with or without petechiae and other purpuric states. They were searched in postmortem bloods and in various body fluids. I have found them in the circulating blood of an

acute lymphatic leukemia with extensive petechiae and ecchymoses I have also found them in the pleural exudates from several cases of acute or subacute pleuritis of an unknown etiology and in the purulent exudate from the peritoneal cavity of a case of chronic tubo-ovarian abscess Doubtless, they are found in various types of inflammatory exudates

Magrath¹ and his co-workers mention "the presence of evident degenerative phenomena in the hemorrhagic cases such as

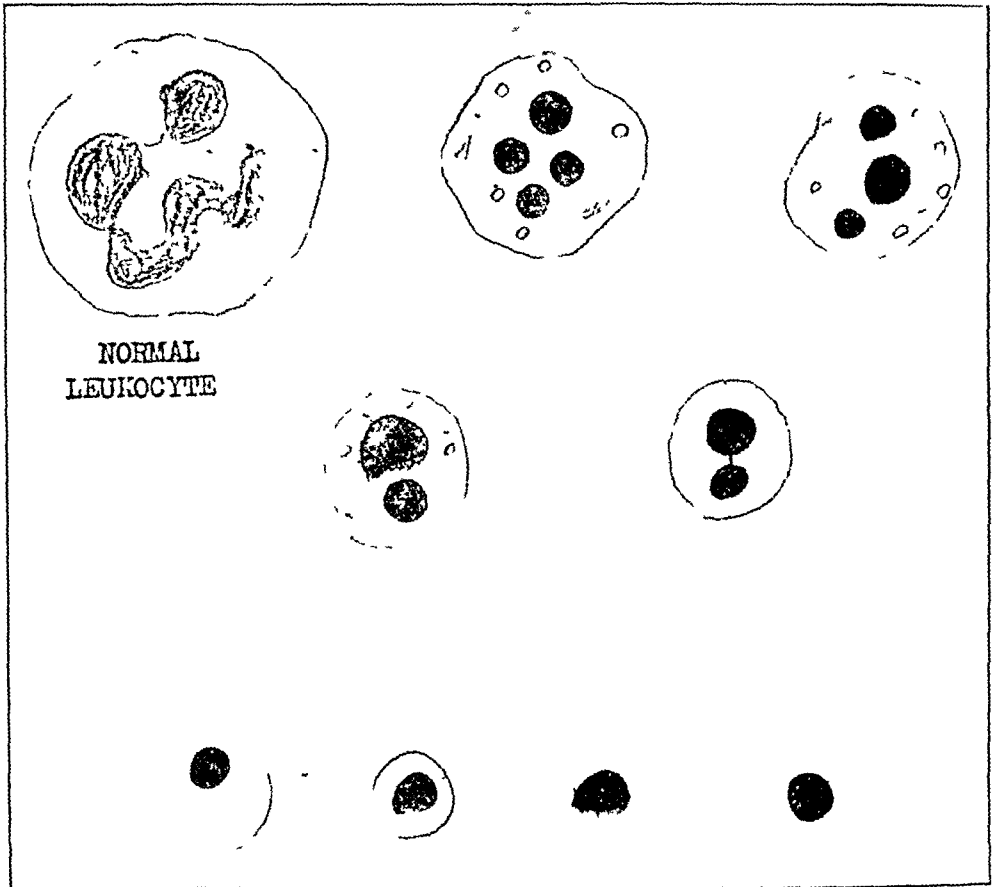


Fig 5—Polymorphonuclear neutrophil leukocytes undergoing degenerative changes present in the blood of purpuric smallpox (schematic drawing) segmentation of nucleus into several darkly staining rounded bodies which gradually diminish in number until finally there is a single dark nuclear body or no neutrophilic cytoplasm

condensation and fragmentation of the nucleus, fragmentation of the whole cells" They do not, however, place any special diagnostic importance on these findings Ferguson⁴ also makes a passing mention of these cells as "the results of degeneration or fragmentation of undoubted polymorphonuclear leukocytes", he calls misleading and unnecessary the name "small pseudolymphocyte neutrophils" as applied to these cells by Weil, but attaches no specific significance to their pres-

⁴ Ferguson, A. R. The Leukocytosis of Variola, *J. Path. & Bacteriol.* 3: 411, 1902

ence Naegeli states that "a complete breaking up of the nucleus into three or four small roundish nuclei can take place during life as a pathologic process Ehrlich first saw this in a case of hemorrhagic smallpox, and it is seen frequently in fresh exudations" ⁵ According to Todd ⁶ these cells are sometimes met with in the blood He says, "The small neutrophilic cell with a single small round deeply staining nucleus which is sometimes encountered must not be confused with the myelocyte Such atypical cells probably result from division of polymorphonuclear neutrophils" However, he fails to cite any specific instances or diseases in which they may occur

In the course of his studies of "the cells in inflammatory exudations" experimentally produced in the peritoneum of guinea-pigs by inoculation of *Bacillus coli* and other pathogenic micro-organisms, Beattie ⁷ found cells of identical morphology from six to seventy-two hours after such inoculations He states, "Some of these cells (polymorphonuclear leukocytes) show the nucleus divided up into a number of small, rounded parts Each of these is uniformly and very darkly stained (twenty-four hours) The polymorphonuclear leukocytes show more of the forms in which the nucleus is broken up into rounded masses stained intensely Some of these cells have broken up, and darkly stained nuclei are seen free (seventy-two hours)"

It is concluded that condensation and fragmentation of the nucleus in the mature leukocytes, already described and discussed, constitutes one of the important, early diagnostic signs Demonstrations of these bodies in the blood smear from a given case with prodromal symptoms of an acute infectious disease, with or without erythematous areas, should be considered as a presumptive evidence of purpuric smallpox In the event of an epidemic, such a demonstration may constitute its positive diagnosis

OTHER CHANGES

Cells of minor importance, such as the monocytes (large mononucleated leukocytes), the eosinophils and the basophils, show no important variations in their number A few investigators, notably, Magrath and Ferguson, state that they have observed an increase in the percentage of the large mononuclear leukocytes of the monocyte type I am inclined to regard at least the majority of these cells as lymphocytes belonging to the slightly early or atypical group An eosinophilia of from 3 to 10 per cent during the first week and of from 15 to 20 per cent on the eighteenth day is reported by Hoffman who studied a large series of cases in Havana This is not supported by other men The

⁵ Ehrlich, P., and Lazarus, A. *Anemia* (translated by H. W. Armit), London, Rebman, 1910, 3 95

⁶ Todd, J. C. *Clinical Diagnosis*, Ed 5, Philadelphia, W. B. Saunders Company, 1924, 3 321

⁷ Beattie, J. M. *The Cells in Inflammatory Exudations. An Experimental Research as to Their Function and Destiny* J. Path. & Bacteriol. 8 129, 1903

eosinophilia in this series may therefore be interpreted as due to the prevalence of intestinal parasites among the natives, or possibly to a peculiar tissue reaction of the natives to the smallpox virus

Various toxic effects on the cytoplasm as are present in the polymorphonuclear leukocytes are noted in these cells

Thrombopenia seems to have little bearing on the coagulability of the blood in any form of smallpox although the coagulation time is definitely hastened during and subsequent to the pustular stage. The bleeding time is appreciably prolonged in purpuric smallpox throughout the course of the disease. This undoubtedly is due to the diminution in the number of platelets coupled with some infectious or toxic process which calls forth the purpuric state and which is not present in the ordinary forms of smallpox

SUMMARY

An analysis of approximately 250 examinations of the blood in all forms of smallpox reveals the following important points

- 1 The blood of the pustular forms of smallpox differs essentially from that of the purpuric form. This is definite and constant and is of value in differential diagnosis

- 2 The platelets are greatly diminished in the initial period in all forms of smallpox. In the pustular forms the greatest diminution is reached in the vesicular stage, followed by a rapid rise through the pustular stage into the desiccation period. In the purpuric form the platelet count shows a consistent downward course until death

- 3 The total leukocyte count shows at the onset an increase, as a rule, in proportion to the severity of the subsequent course of the disease. In the mild pustular forms a definite leukopenia is present in the maculopapular stages. In the severe and fatal pustular forms a high total count is maintained throughout the course of the disease. Its maximum is reached during the early part of the desiccation period. In the purpuric form an initial hyperleukocytosis is steadily maintained. This is considerably higher in the primary type than in the secondary type. There are few exceptions, both in the pustular forms and in the purpuric form, in which a leukopenia or a normal leukocyte count persists throughout the course of the disease

- 4 The polymorphonuclear neutrophil percentage shows a steady downward course in all forms of smallpox except in the desiccation period of the severe and fatal pustular forms. A definite neutropenia of 40 per cent is recorded during the maculopapular stages in the mild form which shows a slight rise during the subsequent stages, declining again to 47 per cent in the desiccation period. A definite polynucleosis is present in the initial and the maculopapular stages in the severe and fatal pustular forms. A decisive neutropenia is obtained in many of the late stages of the purpuric form. The neutrophil fall in this

form is strikingly sudden and spectacular in the presence of a hyperleukocytosis

5 The temperature and the polymorphonuclears run a parallel course while the total leukocyte count shows a reverse curve in all forms of smallpox

6 No characteristic changes are noted either in the hemoglobin or in the erythrocyte count. The fact is of significance in the purpuric form in which there are morphologic and qualitative changes of an advanced anemia, usually accompanied by demonstrable, profuse hemorrhages. A definite secondary anemia may develop in severe pustular and protracted secondary purpuric cases, in which a quantitative decrease of the hemoglobin and of the erythrocytes, together with a proportionate morphologic variation, is demonstrated. The decrease may be of such gravity as to require restorative measures

7 Morphologic changes in the leukocytes and the erythrocytes indicate a severe stimulation of the bone marrow and, in themselves, merely signify various degrees of toxemia or infection. In the blood of the purpuric form, however, there is a series of characteristic metamorphoses in the mature leukocytes which appears to indicate early degenerative changes, specific only in this form of smallpox, and which has served as the only positive laboratory evidence in its diagnosis. This often occurs before any of the clinical signs are evident

CONCLUSIONS

The blood of smallpox shows characteristic findings which, if properly interpreted, are of definite diagnostic and prognostic value

1 The earlier the rise of the platelets, the sooner the approach of the desiccation period, prognosticating a shorter course of the disease

2 A definite leukopenia during the maculopapular stages indicates, as a rule, a mild discrete form. A progressive leukocytosis with an early high polynucleosis predicts a severe form. The higher the values, the more probable the fatal outcome

3 The early appearance of normoblasts, basophilic stippling and polychromatophila, without evident anemia, is an unfavorable sign. It invariably means the purpuric form of smallpox

4 Condensation and fragmentation of mature leukocytes are found only in the purpuric form of smallpox. They appear comparatively early in the primary type of purpuric smallpox and are usually accompanied by pathologic normoblasts, basophilic stippling and polychromatophila, without visible anemia

5 A rapidly progressive, absolute lymphocytosis is a constant characteristic of purpuric smallpox

6 Scarlatinal and other exanthems, infectious purpura and toxic rash with petechiae, etc., can be definitely differentiated from the purpuric form of smallpox during its erythematous stage by these blood findings

GASTRIC SECRETION IN DIABETES MELLITUS

REPORT OF TEN DIABETIC PATIENTS WHO HAD DIARRHEA
AND ACHLORHYDRIA ²

BYRON D BOWEN

AND

A H AARON

BUFFALO

✓ During the last two years one of us has encountered ten diabetic patients with either continuous and uncontrollable diarrhea, or attacks of diarrhea. An analysis of the gastric secretion by the fractional method revealed an achlorhydria in each case

The relationship between the absence of free hydrochloric acid in the gastric contents and a certain type of diarrhea as originally described by Einhorn,¹ who termed it "gastrogenic," is well known. With the advent of the roentgen ray it was possible to study the gastric motility in these cases, and it was noted that the stomach was atonic and emptied rapidly, thus causing a rush of inadequately chymified food into the duodenum. It is the experience of many observers that the diarrhea, in a large percentage of these cases, diminishes or stops with the administration of dilute hydrochloric acid by mouth, even though the administration of the acid does not in any way quantitatively replace the normal amount.

Joslin² regards diarrhea in diabetic patients as a serious complication that demands special attention. He also mentions one patient with diarrhea who was very sensitive to insulin. This remarkable sensitivity, even to small doses of insulin, has been present in three of our patients who had diarrhea and emaciation.

In the literature we were unable to find any comment on the gastric secretion in diabetes. Because of the absence of this information and because of the relatively large number of patients who had diarrhea and achlorhydria, we were prompted to make observations on the gastric secretion in all cases of diabetes.

REPORT OF CASES

CASE 1—*History*—G. C., aged 33, a restaurant keeper, entered the hospital Sept. 1, 1924, and was discharged September 14. He had been a heavy eater and had drunk excessively of alcoholic beverages. He smoked from sixty to seventy cigarettes a day. He had undergone the following operations: a cholecystectomy and appendectomy three years before, a gastro-enterostomy two years before and a hemorrhoidectomy three months prior to admission. He stated that he had had

¹From the Buffalo General Hospital

¹ Einhorn, M. Arch. f. Verdauungskr. 3 133, 1898

² Joslin, E. P. The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1923, p. 597

diarrhea ever since the operation two years before, sometimes reaching fifteen movements a day, also, that six months before he developed thirst, frequent urination and a voracious appetite. During that period his weight dropped from 145 to 128 pounds (65.8 to 58.1 Kg.)

Physical Examination—This showed a rather restless and slightly emaciated man. The skin showed considerable pallor. Marked gingivitis was present. The tonsils were enlarged, and the cervical lymph nodes were palpable. The accessible arteries and veins showed marked thickening and the blood pressure was 90 mm systolic and 60 diastolic.

Laboratory Findings—The urine showed a slight trace of albumin, sugar, + + +, no ketones, the sediment was negative. The hemoglobin was 72 per cent, red blood cells, 4,000,000, and white cells, 6,500 per cubic millimeter. The blood urea nitrogen was 16 mg and the sugar 300 mg per hundred cubic centimeters. The Wassermann reaction in the blood serum was negative. Fractional analysis of the gastric contents after an Ewald meal showed an achlorhydria in all specimens with a total acidity varying from 22 to 38 degrees. The feces showed a + + benzidin reaction on two occasions, no ova or parasites were found on three examinations. The stools were very large and "soapy" and when stained with sudan III showed an enormous increase in neutral fat.

Fat Excretion (Dr. Anne Viele)—While the patient was receiving a diet of 70 Gm of carbohydrate, 62 Gm of protein and 170 Gm of fat, the weight of the twenty-four hour feces was 882 Gm. The total amount of fat excreted as determined by the Bloor method was 94 Gm, which represented 55 per cent of the ingested fat.

Course—The patient was discharged from the hospital on a diet of 70 Gm of carbohydrate, 62 Gm of protein and 170 Gm of fat, which gave 2,058 calories. His urine was free from sugar and his blood sugar during digestion was 200 mg. Fourteen units of insulin was given half an hour before each meal and 2 cc of dilute hydrochloric acid with each meal. He was followed after his discharge from the hospital for about two months during which time he improved rapidly, remaining free from sugar most of the time but still having from five to ten bowel movements daily. His weight, October 24, was 146 pounds (66.2 Kg.), a gain of 18 pounds (8.2 Kg.). It was learned later that he became careless with regard to his habits of eating and drinking although he continued with the use of insulin most of the time. April 1, 1925, he developed lobar pneumonia and died on the seventh day. Unfortunately, permission for a necropsy was not granted.

This case probably represents a total pancreatitis involving both the external and the internal secretions and also a hyposecretion of the gastric mucosa.

CASE 2—J. D., aged 55, a housewife, entered the hospital Nov. 2, 1922, and was discharged Jan. 22, 1923. She had had pulmonary tuberculosis of both lungs, chiefly the right, twenty-six years before, for which she had spent considerable time, off and on, at a sanatorium in the mountains. She also stated that she had had attacks of diarrhea lasting for several days for the last year. Two years prior to admission diabetic symptoms began with a rather rapid loss of weight, which dropped from 175 to 100 pounds (79.4 to 45.4 Kg.) on admission.

Physical Examination—The patient was a thin, poorly nourished woman with dry, warm skin. The right lung showed involvement throughout, with dulness, bronchophony and whispered pectoriloquy in the scapular area only. There were many coarse, crepitant râles throughout. There also were a few râles in the left mammary region. The arteries and the veins were thickened, the former being tortuous. The temperature during her stay in the hospital was usually normal but occasionally went to 99.5 during the afternoon. The pulse was usually around 80. The blood pressure was 120 mm systolic and 75 diastolic.

Laboratory Findings—The urinalysis was found to be negative on several examinations with the exception of the presence of sugar and ketones. The blood showed 80 per cent hemoglobin, 8,000 white cells, with 81 per cent of polymorphonuclears. The Wassermann reaction in the blood serum was negative. The sputum on twenty examinations did not show any tubercle bacilli. The blood sugar was found to range between 190 and 290 mg per hundred cubic centimeters.

Course—The patient was discharged on a diet of 63 Gm of carbohydrate, 36 Gm of protein and 182 Gm of fat, taking $12\frac{1}{2}$ units of insulin twice a day. The urine remained free from sugar and her blood sugar during digestion was 200 mg. She had been in the hospital for more than two months and despite the fact that her diet had been fairly liberal, and that she had been kept free from sugar most of the time, her weight had dropped to 91 pounds (41.3 Kg). Some of this, however, was probably loss of fluid. After her discharge, she was seen occasionally for about six months and it was found that she had become very careless about her diet. Nevertheless, her weight increased to 102 pounds (46.3 Kg). The patient was not seen again until January, 1924, when she was admitted to the hospital in a state of impending coma. After she had made a successful recovery from this, her weight was found to be 99.75 pounds (45.2 Kg). It was determined that her attacks of diarrhea had been especially annoying and frequent since her discharge a year before. A fractional analysis of the gastric contents showed at that time a complete achlorhydria in all specimens and a variation in the total acidity from 8 to 15 degrees. Dilute hydrochloric acid, 2 cc., was given with the meals and half an hour after. She was discharged from the hospital, January 13, on a diet of 70 Gm of carbohydrate, 50 Gm of protein and 150 Gm of fat, receiving 20 units of insulin half an hour before each meal. She remained on that program for ten months during which time her weight increased up to 159 pounds (72.1 Kg) and her attacks of diarrhea entirely disappeared. She had, however, recently omitted the hydrochloric acid entirely without any recurrence of diarrhea. July 1, 1925, the gastric contents were again examined by the fractional method with the result that complete achlorhydria was still present. Her weight at this time was 165 pounds (74.8 Kg).

This case presents several features of interest. First, although irrelevant to the present paper, diabetes followed pulmonary tuberculosis, the tuberculosis, however, was of the chronic fibroid type. Second, the patient did not improve nor gain appreciably in weight during the first year of treatment while receiving 25 units of insulin daily and while having frequent attacks of diarrhea. Later, when the dosage of insulin was increased to 60 units a day and dilute hydrochloric acid was given, the weight increased by 60 pounds (27.2 Kg) in ten months and the diarrhea disappeared not to recur even though the acid was omitted. As had been expected, the gastric acidity remained the same. It is probable that the eradication of the diarrhea and the increased dosage of insulin improved the patient's nutritional state.

CASE 3—T. B., aged 40, a business man, was admitted to the hospital, Aug 30, 1924, and died Nov 9, 1924. The past history was unimportant except that he had been afflicted with many boils and abscesses ten years before. Diabetic symptoms began six years before and since that time he lost 70 pounds (31.8 Kg) in weight, his weight on admission being 76 pounds (34.5 Kg). He had been under treatment in two other hospitals, in one of which he had received insulin. However, he was not faithful to the treatment after his discharge because there did not seem to be any improvement. During the last year he reported that his bowels had been moving from two to six times daily but that during the last few months, the number of movements had increased, sometimes reaching fifteen.

Physical Examination—The patient was an extremely emaciated man apparently in no discomfort, whose skin was exceedingly dry and wrinkled. The teeth had been extracted and the patient was not wearing the plates that had been made for him. The tongue was dry and smooth. The heart showed a soft systolic murmur at the apex which was not transmitted. The blood pressure was 88 mm systolic and 72 diastolic. The knee jerks and ankle jerks could not be elicited.

Laboratory Findings—The urine on admission showed a trace of albumin, and in one specimen a rare hyaline cast. It contained sugar but no ketone bodies. The blood contained 52 per cent of hemoglobin, 3,210,000 red cells and 3,300 white cells, 72 per cent of which were polymorphonuclears. The Wassermann reaction in the blood serum was negative. Fractional analysis of the gastric contents showed no free hydrochloric acid in five specimens collected at twenty-minute intervals. The total acidity, however, increased from 12 to 44 degrees. The basal metabolic rate was plus 1 per cent. The blood sugar was 180 mg per hundred cubic centimeters.

Pancreatic Enzymes (Dr J V Wadsworth)—The activity of the pancreatic enzymes was studied by the McClure method both when the patient was fasting and after a test meal of 50 cc of cream into the duodenum. The results are given in Table 1.

All specimens of the duodenal contents were found to be strongly acid and there apparently was rapid emptying of the stomach. Trypsin and steapsin are

TABLE 1—*Pancreatic Enzymes*

	Trypsin, Mg of Nonprotein Nitrogen	Steapsin Cc of Tenth Normal Sodium Hydroxid	Amylopsin, Mg of Glucose
Fasting or resting contents	1.3	0.5	3.0
Test meal 50 cc cream by mouth			
One half hour	1.2	0.3	2.0
One hour	9.6	0.2	5.0
Two hours	1.8	0.6	2.0
Normal values	5.0-10.0	2.5-6.0	3.0-10.0

present but reduced from one third to one fourth of the normal values. This reduction is possibly caused by the acidity of the duodenal contents. Amylopsin was present in normal amounts.

Fat Excretion (Dr Anne Viele)—The fat ingesta in the diet was 150 Gm during the twenty-four hours. The weight of the feces in twenty-four hours was 235 Gm, which was found to contain 10 Gm of total fat representing 6.75 per cent of the ingested fat.

Course—The patient was given a diet of about 1,000 calories and 3 units of insulin before meals. In a few days insulin was increased to four units whereon he developed a severe insulin shock and deep coma. He, however, responded immediately to glucose intravenously. The diet was increased to about 2,000 calories but he would never tolerate more than 4 units of insulin three times a day. The urine remained free from sugar except for an occasional trace in the forenoon specimen. The blood sugar during digestion ranged between 122 and 250 mg. There was no increase in weight. The diarrhea continued without any abatement despite treatment with dilute hydrochloric acid three times a day, bismuth, and at times tincture of opium. October 2, the patient complained of frequency and urgency of urination. The urine was found to contain a large amount of albumin, and pus in the sediment. Several days after that, the patient developed vesical retention and had to be catheterized. October 8, the urologic department made a diagnosis of a "spinal cord bladder" and recommended an indwelling catheter and irrigations twice daily. October 21, the patient developed fever which continued for several days. November 4, an area of redness appeared on the left buttock. November 8, this had developed into an abscess so that it

required drainage. The patient was getting progressively weaker and at times refused to eat. Death occurred, November 9.

Necropsy (Dr Benjamin Roman) —There were extreme atrophy of the pancreas, which weighed 37 Gm with considerable fat tissue included, and high grade general emaciation. Diabetes mellitus was diagnosed. The necropsy also revealed atrophy of the brain with external and internal hydrocephalus and edema of the brain, degeneration of the posterior columns of the cord (tabetic form), brown atrophy of the heart and of the liver, atrophy of the kidneys and of the spleen, large decubitus ulcer and two abscesses in the region of the sacrum (one opened surgically), multiple abscesses of the left kidney, moderate hydrops, ascites, hydrothorax and hydropericardium, edema of the gastro-intestinal mucosa, slight catarrhal cystitis, pressure necrosis in the prostatic urethra, total adhesive pleurisy on the left side with a 10 by 4 cm osteoma embedded in the thickened pleura, and swelling and contractures of both knee joints.

This patient represents one of those severe cases of diabetes with diarrhea in which the patient can tolerate only very small doses of insulin despite an abundant diet. The hypermotility of the gastro-intestinal tract and unsatisfactory absorption account in some measure for the failure to improve. The stools showed a large amount of undigested material, but, curiously enough, the total fat excreted was only slightly in excess of normal. The external secretion of the pancreas appeared to be present but there was a complete achlorhydria of the gastric secretion. A "spinal bladder" was diagnosed during life and a degeneration of the posterior columns of the cord was found at necropsy. There was no evidence either of syphilis or of pernicious anemia. The patient developed a decubitus ulcer with secondary sepsis which was the immediate cause of death.

DESCRIPTION OF THE TABLES

The cases are divided into three groups. Table 2 contains all cases that showed a complete absence of free hydrochloric acid in all specimens. The cases showing free hydrochloric acid to be absent only in the first few specimens, those in which free hydrochloric acid was present in traces or never exceeded 15 degrees in any specimen are listed in Table 3 under the gastric subacidity group. The patients on whom a normal gastric secretion was found are shown in Table 4.

All patients are listed with relation to the probable duration of the disease beginning with the longest. The severity of the diabetes was crudely estimated by the following symbols which were used in a previous article³

Plus-minus (\pm) = patients with mild diabetes

One plus (+) = patients in whom the diabetes was controlled by diet

Two plus (++) = patients requiring small doses of insulin

Three plus (+++) = patients requiring large doses of insulin to control the diabetes

3 Bowen, B. D., Koenig, E. C., and Viele, A. A Study of the Lower Extremities in Diabetes as Compared with Nondiabetic States, from the Standpoint of X-Ray Findings, with Particular Reference to the Relationship of Arteriosclerosis and Diabetes, *Bull. Buffalo Gen. Hosp.* 2:35 (April) 1924.

COMMENT

A fractional gastric analysis has been made on a series of sixty-nine diabetic patients. These patients have been taken at random, for the most part within the last six months. However, Cases 15, 10, 4 and 1 were encountered before the gastric analyses were reduced to a routine

TABLE 2—*Diabetic Patients with Achlorhydria*

Case	Age	Sex*	Probable Duration of Diabetes	Severity of Diabetes	Remarks
1	64	♀	20 years	+++	Chronic nephritis, arterial hypertension, died
2	61	♀	15 years	++	Arteriosclerosis, died from coronary thrombosis
3	64	♀	14 years	+++	Diarrhea, relieved by hydrochloric acid
4	35	♀	12 years	+++	Diarrhea, not relieved by hydrochloric acid
5	55	♀	10 years	+++	Arteriosclerosis, cellulitis of the foot
6	57	♀	9 years	++	Retinitis, diarrhea, relieved by hydrochloric acid
7	69	♀	8 years	++	Gallbladder disease, arteriosclerosis
8	55	♀	7 years	+++	Diarrhea, relieved by hydrochloric acid, died from acute pulmonary tuberculosis
9	39	♂	6 years	+++	Diarrhea, not relieved by hydrochloric acid, extreme emaciation, died
10	55	♀	5 years	++	Diarrhea, relieved by hydrochloric acid
11	48	♀	5 years	++	Arterial hypertension
12	42	♂	3 years	+++	Diarrhea, not relieved by hydrochloric acid, extreme emaciation, died
13	55	♀	3 years	+++	Diarrhea, relieved by hydrochloric acid, fibroid phthisis
14	51	♂	3 years	+++	Precoma
15	62	♀	3 years	++	Diarrhea, relieved by hydrochloric acid
16	33	♂	2 years	+++	Diarrhea, not relieved by hydrochloric acid, statorrhea, died of lobar pneumonia
17	51	♀	2 years	+++	Achlorhydria on a single specimen, coma
18	53	♂	2 years	+++	Had been obese, had marked loss of weight, advanced pyorrhea
19	46	♂	1 year	+++	Arteriosclerosis
20	59	♀	1 year	+++	Arteriosclerosis

* In this and the succeeding tables, ♂ indicates male, ♀, female

TABLE 3—*Diabetic Patients with Gastric Subacidity*

Case	Age	Sex	Probable Duration of Diabetes	Severity of Diabetes	Remarks
21	35	♀	8 years	+	Extreme obesity without loss of weight
22	57	♀	7 years	++	Diabetic "neuritis"
23	58	♀	7 years	+++	Gained 70 pounds (31.8 Kg) after insulin was given
24	31	♂	6 years	+++	
25	56	♀	5 years	++	Pulmonary tuberculosis, gallbladder disease
26	64	♀	5 years	+	Arteriosclerosis, chronic nephritis
27	56	♀	4 years	+	Arterial hypertension
28	51	♀	3 years	++	Arteriosclerosis
29	34	♀	2 years	+++	Three times in coma
30	58	♀	1 year	++	Premature ventricular contractions
31	36	♀	1 year	++	Catact which disappeared with insulin
32	25	♂	1 year	++	
33	52	♀	4 months	++	Extreme obesity, chronic myocarditis
34	50	♂	2 months	+++	Carcinoma of head of pancreas, died

On the other hand, gastric analyses have been made on quite a number of earlier patients recently. Because of this it is difficult, if not impossible, to state whether or not these cases which are being reported are representative of other cases had they been chosen in strict succession as they entered the hospital. Also it is more than likely that cases seen in a general hospital are probably more severe and have more compli-

cations than the average of a large number of diabetic patients. In addition, it seems improbable that ten patients with diabetes having diarrhea would ordinarily be encountered in a group of sixty-nine patients. Therefore, it is our impression that this group cannot be judged to be entirely representative, notwithstanding the fact that gastric analyses have been done on all patients who would give us permission, including those who have been admitted to the hospital during the last six months and those who are available from the outpatient department.

The cases showing achlorhydria were 29 per cent of those studied. It can be readily seen by glancing through Table 2, which contains this

TABLE 4—*Diabetic Patients with Normal Gastric Secretion*

Case	Age	Sex	Probable Duration of Diabetes	Severity of Diabetes	Remarks
35	70	♀	15 years	+	Arteriosclerosis
36	49	♀	12 years	+	Obesity
37	52	♀	8 years	++	Thyroid adenoma
38	64	♀	5 years	++	Marked loss of weight
39	64	♀	5 years	++	Obesity
40	46	♀	5 years	+++	
41	65	♀	4 years	+	Arterial hypertension, gallbladder disease
42	62	♀	4 years	++	Arterial hypertension, gangrene of foot
43	26	♀	4 years	+++	
44	57	♀	3 years	+++	Arterial hypertension, glaucoma
45	55	♀	3 years	++	
46	55	♀	3 years	++	Gallbladder disease
47	48	♀	3 years	+	Arterial hypertension
48	31	♀	2 years	++	
49	70	♀	2 years	++	Arterial hypertension, old hemiplegia
50	63	♀	2 years	++	
51	60	♀	18 months	+	
52	11	♀	14 months	+++	Twice in coma
53	52	♀	1 year	+	
54	56	♀	1 year	+	Gangrene of foot
55	32	♀	1 year	+++	Admitted in coma
56	48	♀	1 year	++	Arteriosclerosis
57	56	♀	1 year	+++	Arteriosclerosis
58	56	♀	1 year	+	Slight arterial hypertension
59	59	♀	1 year	+	Arterial hypertension
60	50	♀	1 year	++	Arthritis deformans
61	53	♀	6 months	+	Obesity
62	53	♀	6 months	+	Slight obesity
63	67	♀	6 months	+	
64	39	♀	5 months	+	Obesity
65	34	♀	3 months	+	Extreme obesity, chronic myocarditis
66	43	♀	3 months	++	
67	75	♀	5 weeks	++	
68	36	♀	4 weeks	++	
69	54	♀	4 weeks*	+	Arterial hypertension, hysteria

* No diabetic history, sugar discovered on admission

group, that there is no patient having achlorhydria who did not have either severe or long standing diabetes, or both. On the other hand, this statement was by no means found to be reversible, because both the subacidity and the normal groups contain cases of long duration with severe diabetes.

In other words, achlorhydria was not found in any patient who had mild diabetes nor in any patient who had had diabetes for less than a year. However, it was stated that in Case 19 the diabetic symptoms had been present only a year. Notwithstanding this, it is probable,

because of the loss of weight and the rather advanced arteriosclerosis, that the diabetes was of considerably longer duration

The average duration in the achlorhydria group was 6.6 years, in the subacidity group, 3.6 years, and in the normal group, 2.8 years. In the normal group there are a few cases of quite long duration. Case 37 of eight years' duration was possibly one of thyroid adenoma with glycosuria that later developed into diabetes. Case 39, of five years' duration, was one of obesity. Case 38, of five years' duration, had been mild until the last year. Case 36, of twelve years' duration in a patient with obesity, was apparently mild because there had been little loss of weight and no loss of tolerance during the last four years. Case 35, of fifteen years' duration, was a mild diabetes and a marked senile arteriosclerosis.

Furthermore, it is to be noted that six of the twenty cases with achlorhydria proved fatal while only one of the cases in the gastric subacidity group was fatal, death being due to carcinoma of the pancreas. All the other patients with normal gastric secretion are still living. This, however, may be misleading because, as was stated above, our first observations were only on diabetic patients who had diarrhea and it was in these patients that the majority of deaths occurred. Also, the analyses in the majority of instances have been made so recently that they comprise mostly patients who are doing well. Nevertheless it is significant that 30 per cent of the patients on whom achlorhydria was found died—mostly, as will be noted, from causes possibly secondary to or contributed by rather long standing and uncontrolled diabetes.

Diarrhea was not found in any diabetic patient unless achlorhydria existed and diarrhea occurred in ten out of twenty patients who were found to have achlorhydria. The diarrhea in every case was antedated by the diabetes, usually by a number of years. One of these, Case 16, was one of involvement of both the insular and the acinous portions of the pancreas. In Case 9, the study of the fat excretion before death and the findings of the necropsy would not indicate any involvement of the acini. In Case 12, no studies of the fat excretion were made and permission for a necropsy was not gained. Patient 4, who had had diabetes for twelve years and diarrhea for two years before insulin was started in 1923, had gained from 111 to 143 pounds (50.3 to 64.9 Kg.), during which time he had been taking 40 units of insulin a day and dilute hydrochloric acid with his meals. The diarrhea had not changed perceptibly although there are times when it is absent for several days. Also, in this case, the reduction in the amount of fat in the diet has been tried without any noticeable effect on the number or the character of the movements. Of the ten patients who had diarrhea, four have died, one is not improved, and in six the diarrhea disappeared coincidentally with the use of dilute hydrochloric acid. However, the omission

of hydrochloric acid after it had been taken for several months did not effect a return of the diarrhea. Two patients (Cases 17 and 14) who have achlorhydria without diarrhea have been treated with dilute hydrochloric acid for a period of about two months with no improvement in their condition other than would have been expected with insulin alone.

The majority of the patients studied have exceeded the age of 40 years. The average age in the achlorhydria group is 50.7 years, in the normal, 51.1 years, and in the subacidity group, 47.2 years. The youngest patient studied was 11 years and the oldest 75 years, both had normal gastric acidity.

It is unfortunate that we have not tested for the presence of pepsin in every case showing an absence of free hydrochloric acid. Therefore, it is impossible for us to state whether our cases were achlorhydria or true achylia gastrica. However, in several cases only a trace of pepsin was found and in one, Case 10, it was entirely absent. The method of Mett as modified by Nirenstein and Schiff⁴ was used, the Mett tubes being prepared by Christiansen's⁵ method.

The incidence of achlorhydria in 325 consecutive fractional test meals was found by Hurst⁶ to be 10.5 per cent. In a larger series (2,730 cases) Eggleston⁷ has reported achlorhydria in 10 per cent. Both call attention to the necessity of using the fractional method of analysis in the diagnosis of true achlorhydria and state that if the single examination were used, the incidence of achlorhydria would be about 9 per cent higher. It is assumed that the cases referred to in these statistics represent both normal and pathologic material. Bennett and Ryle,⁸ in a series of fractional gastric analyses on 100 normal subjects, encountered complete absence of free hydrochloric acid in four.

Achlorhydria or achylia gastrica apparently is a condition having a multiple etiology. Its relationship to some diseases such as gallbladder disease, advanced pulmonary tuberculosis, gastric ulcer, hepatic disease, carcinoma of the stomach, or repeated attacks of acute gastritis appears to be secondary. In five cases of carcinoma of the pancreas, one of probable carcinoma and chronic inflammation of the pancreas and in one case in which a definite diagnosis of chronic pancreatitis had been made, Bell⁹ has found a complete absence of free hydrochloric acid in

4 Nirenstein and Schiff, in Hawk, P. B. *Practical Physiological Chemistry*, Philadelphia, P. Blakiston's Son & Co., 1918, pp. 169 and 170.

5 Christiansen, in Hawk (Footnote 4).

6 Hurst, A. F. Achlorhydria. Its Relation to Pernicious Anemia and Other Diseases, *Lancet* **1** 111 (Jan. 20) 1923.

7 Eggleston, E. L. Gastric Secretory Disturbances, *Bull. Battle Creek San and Hosp. Clinic* **20** 89 (May) 1925.

8 Bennett, T. I., and Ryle, J. A. Studies in Gastric Secretion, *Guy's Hosp. Rep.* **71** 286 (July) 1921.

9 Bell, J. R. Consecutive Series of 425 Gastric Analyses by the Fractional Method, *Guy's Hosp. Rep.* **72** 302 (July) 1922.

all specimens. He comments on this finding as probably being more than a mere coincidence. In pernicious anemia, the absence of hydrochloric acid in the gastric secretions apparently precedes the recognizable symptoms of the disease. At this point it is of interest to call attention to the extreme rarity of diabetes mellitus associated with pernicious anemia, as was recently commented on by Adams¹⁰

In analyzing the complications and associated diseases of all the cases in the three groups, it does not seem that the recognized causes of achlorhydria are more frequent in the achlorhydria group. In Case 8 the pulmonary tuberculosis was acute and developed after the achlorhydria had been found. In Case 13, fibroid phthisis had probably been present for many years and might have contributed to achlorhydria. It is possible if not probable that gallbladder disease was present in a larger number of patients than was indicated, because we have relied entirely on the characteristic history and physical findings found in that disturbance. In this group, Case 7 was the only one in which such a diagnosis could definitely be made.

According to the observations of McClure, Montague and Mortimer,¹¹ there does not appear to be any reduction in the enzymic activity of the pancreas in cases of achlorhydria. In a study of the enzymic activity of the pancreatic secretion in a group of sixty-eight diabetic patients, Jones, Castle, Mulholland and Bailey¹² have concluded that there was marked alteration of the external secretory function. They believe that this abnormality is related to the functional or anatomic changes in the acinous tissue of the pancreas and suggest that this diminution may interfere with the proper digestion of protein and fat. They also report that the bile pigment elimination was abnormally high in about 75 per cent of their cases. These findings, in addition to our observations, suggest that possibly in diabetes mellitus there is an abnormality of the entire digestive system.

SUMMARY

1 Fractional gastric analyses have been made on sixty-nine diabetic patients. On critical analysis this group cannot be considered as strictly representative of diabetes as it would be seen in a large group of cases,

10 Adams, S. F. Three Cases of Pernicious Anemia and Diabetes Mellitus with a Note on the Apparent Ineffectiveness of Insulin in the Presence of a Profound Anemia, *M. Clin. N. A.* **8** 1163 (Jan.) 1925.

11 McClure, C. W., Montague, O. C., and Mortimer, E. Pancreatic Function in the Absence of Free Hydrochloric Acid from the Stomach, *Boston M. & S. J.* **190** 357 (Feb. 28) 1924.

12 Jones, C. M., Castle, W. B., Mulholland, H. B., and Bailey, F. O. Pancreatic and Hepatic Activity in Diabetes Mellitus. The Alterations with Some Observations on the Etiology of the Disease, *Arch. Int. Med.* **35** 315 (March 15) 1925.

because of the inclusion of a number of patients who were studied some time before on account of diarrhea, and also because the majority were hospital cases which are possibly more severe than the average

2 A complete absence of free hydrochloric acid was found in twenty patients, or 29 per cent. Of these, ten had diarrhea while no cases of diarrhea were found in which the patients had free hydrochloric acid. The artificial use of dilute hydrochloric acid did not appear to affect the diarrhea in four patients, three of whom died, one having marked steatorrhea. In the other six patients, the diarrhea stopped coincidentally with the use of the acid, but did not reappear when the acid was withdrawn. The patients, however, in all instances took the acid over a period of several months. There was no reappearance of free hydrochloric acid in one case (Case 13) that was subsequently studied.

3 Of the twenty patients who had achlorhydria, the average duration of the diabetes was 6.5 years and diabetes was severe in every case at the time of observation. The duration in the normal group was 28 years while the gastric subacidity group held the middle position, with an average of 3.6 years. There was no essential difference in the average ages of the patients in the three groups.

4 In an analysis of the complicating factors in each case, it does not appear that the conditions that are known to produce achlorhydria in nondiabetic subjects are more prevalent in the achlorhydria group.

5 From the results of these observations it seems justifiable to presume that achlorhydria may be the result of long standing or severe diabetes.

HEMOGLOBIN, COLOR INDEX, SATURATION INDEX AND VOLUME INDEX STANDARDS

REDETERMINATIONS BASED ON THE FINDINGS IN ONE HUNDRED
AND THIRTY-SEVEN HEALTHY YOUNG MEN *

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The value of color index, volume index and hemoglobin determinations in the differential diagnosis of anemias is well known. But the absence of correct normal standards for the number, volume and hemoglobin content of red cells and the inaccuracy of almost all the clinical hemoglobin methods is a great handicap.

Kern¹ calls attention to the number of widely different hemoglobin figures used as 100 per cent by various authors and instrument makers (e g, 13.8, 15.0, 15.6, 16.92 and 17.3 Gm of hemoglobin per hundred cubic centimeters of blood). He emphasizes the importance of knowing the normal amount of hemoglobin per hundred cubic centimeters of blood calculated to a count of 5 million red cells, since this figure forms the basis for the calculation of the color index. Brown and Rowntree² state "The normal standard of hemoglobin is as yet unsettled, this is somewhat surprising in a substance so important."

When our attention was first directed to this problem in the spring of 1919, we, too, were surprised at the scarcity of work on this subject. A study of the available methods of estimating hemoglobin explained everything. These methods were either too inaccurate for research purposes or so technical and time consuming that the labor involved in studying an adequate number of cases was prohibitive. Thus, our first effort was to perfect an accurate, simple method of estimating hemoglobin which would be satisfactory for clinical as well as research use. The method of Osgood and Haskins³ has made the present study possible.

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1 Kern, R. A. Problems of Clinical Hemoglobin Estimation, *M. Clin. N. Am.* **8**: 821 (Nov.) 1924

2 Brown, G. E., and Rowntree, L. G. The Volume and Composition of the Blood and the Changes Incident to Diuresis in Cases of Edema, *Arch. Int. Med.* **35**: 129 (Jan.) 1925

3 Osgood, E. E., and Haskins, H. D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* **57**: 107 (Aug.) 1923

METHODS

Preliminary—All tests were made on venous blood, drawn by the usual technic. Exactly 10 cc of blood was quickly and thoroughly mixed with exactly 20 mg⁴ of finely powdered, neutral potassium oxalate to prevent clotting. We strongly recommend the use of oxalated venous blood for all color index and volume index determinations. Our use of such blood guarantees exactly the same concentration of red cells in the portion of blood used for hemoglobin estimation, or for red cell volume determination, as in the portion used for the red cell count. Using separate drops from the ear or finger does not give us any such assurance of uniformity.

Red Cell Counts—From two to four closely agreeing counts were made on each blood, under my direct supervision, by medical students especially trained for this work. Their results were accepted for this study only after they were able to get duplicate counts varying by less than 100,000 cells per cubic millimeter with regularity. Counting chambers with Levy-Neubauer rulings (tested by the Bureau of Standards) were used. The pipets were carefully recalibrated. Well mixed blood was diluted 1 part in 200 with Toisson's solution and the pipet shaken thoroughly before the counting chamber was filled. After from three to five minutes settling the cells in 100 small squares were counted. The average of the counts on from two to four dilutions of the same blood is the red cell count reported. If the cells were unevenly distributed or if duplicate counts did not agree closely, the results were discarded and all the counts were repeated. We feel that a maximum error of 3 per cent in our reported counts is a conservative estimate.

Cell Volume—This was determined by centrifugating about 4 cc of the oxalated blood in a special tube at over 4,500 revolutions per minute until the cell volume remained constant. After an initial period of from twenty to thirty minutes the blood was centrifugated for five minute periods until successive readings showed no change in volume. This is a necessary precaution owing to the great variations in sedimentation time. Most bloods will be completely sedimented in one-half hour at this speed, but a few require more than one hour. The centrifuge tube that we used was prepared by sealing the tip of a 10 cc Mohr pipet (graduated to the tip) and cutting it off a little above the 6 mark (capacity, 4 cc). It was carefully recalibrated. Fitted with corks as shown in figure 1, it is well supported by the ordinary centrifuge tube holder. Such a narrow tube permits of accurate readings on 3 or 4 cc of blood. However, if 10 cc of blood is available, satisfactory

4 For ordinary clinical purposes 1 drop of 30 per cent potassium oxalate solution is satisfactory.

estimations can be made in an ordinary graduated centrifuge tube. This must, of course, be recalibrated. The possible objection to our manner of using potassium oxalate is answered and other methods of cell volume determination are discussed elsewhere in this paper.

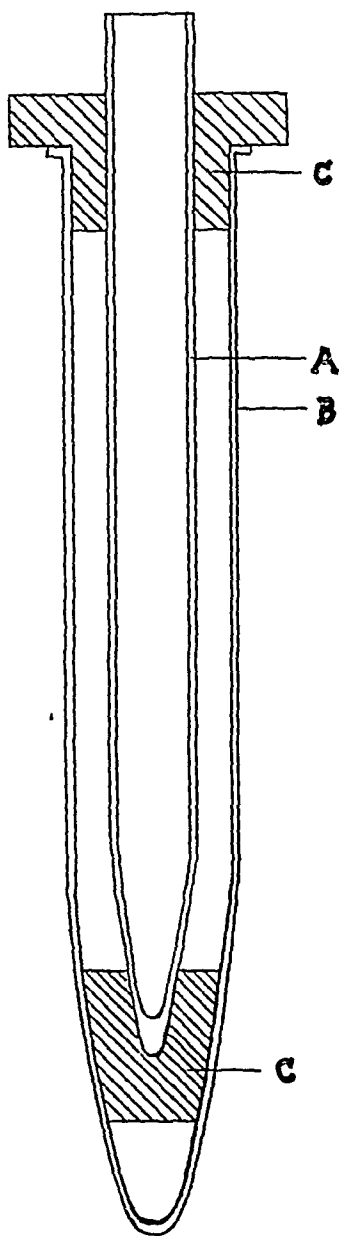


Fig 1—Tube used in centrifugating, A, tube, B, holder, C, corks to act as supports

Hemoglobin Estimations—Hemoglobin was estimated by our own method⁵. The hemoglobin was converted into acid hematin by first taking exactly 1 cc⁵ of well mixed oxalated blood with about 45 cc of distilled water in a 100 cc flask, and then treating with 50 cc of one-

⁵ As little as 0.05 cc may be taken, if 2.45 cc of water and 2.5 cc of acid are used. Greater accuracy is insured by our larger quantities.

fifth normal hydrochloric acid (18 cc of chemically pure acid diluted to 1 liter is satisfactory) After diluting to the mark and mixing, the maximum acid hematin color was developed by heating a test tube full in a water bath kept at about 55 C for seven minutes (or the acid hematin may stand twenty-four hours at room temperature in the dark) The cooled solution was then compared with our permanent standard (set at 15 mm) in a Kober colorimeter⁶ by artificial light The temperature of the standard was taken with a reliable thermometer after each reading The percentage of hemoglobin (100 per cent by our method means that the blood contains 13.8 Gm of hemoglobin per hundred cubic centimeters and has an oxygen capacity of 18.5 cc) was read from our

TABLE 1—*Comparison of Estimations of Hemoglobin by Osgood and Haskins' Method and by Van Slyke's Method*

Blood No	Percentage of Hemoglobin	
	New Method	Van Slyke's Method*
1	29.7	30.6
2	37.0	36.8
3	43.7	42.9
4	49.7	49.0
5	56.0	56.0
6	61.0	61.3
7	65.7	66.0
8	72.3	74.0
9	80.4	79.8
10	90.8	91.9
11	96.2	96.7
12	100.5	100.0
13	104.8	104.6
14	117.3	116.8
15	123.2	122.6
16	131.3	132.2

* We found it necessary to take the mean of several Van Slyke estimations in order to keep the probable error below 1 per cent. The results by our method given above are also the mean of several determinations.

special table in the column under the temperature of the standard solution and opposite the colorimeter reading. The results reported were based on the average of four such readings, but were calculated to grams of hemoglobin per hundred cubic centimeters. Certified pipets and flasks were used for all measurements.

The accuracy of our method was proved by comparison with Van Slyke's⁷ latest method (the accepted standard research method). Table 1 shows that in only one case is the difference as great as 1 per cent between the result by our method and the average of several estimations by the

6 The colorimeter and lamp were kept in fixed positions, so that the colorimeter was always in proper adjustment for the estimation. The use of daylight involves frequent resetting of the colorimeter.

7 Van Slyke, D. D., and Stadie, W. C. The Determination of the Gases of the Blood, *J. Biol. Chem.* 49:1 (Nov.) 1921.

Van Slyke technic The maximum error, therefore, in any one of our hemoglobin estimations is certainly not over 2 per cent

We wish to emphasize the fact that all the methods we have used, while of research accuracy, are also clinically practical None is too time consuming or too difficult for any careful technician Furthermore, these methods do not require extra apparatus not found in every well equipped clinical laboratory

SUBJECTS EXAMINED

One hundred and thirty-seven male medical students between the ages of 19 and 30 were studied The age, height, weight and nationality of each was recorded As no use has been made of the height and weight figures in this paper they are omitted The majority were American born of American parents Most of the others were American born of foreign born parents Aside from American, the nationalities chiefly represented were English, Scotch, Scandinavian and German These subjects, we believe, furnish a fair cross-section of the population of this sex and age in the Pacific Northwest There were not enough men of any one nationality to justify an analysis on this basis, so the nationalities are not reported

Each man considered himself perfectly healthy at the time the blood was drawn, and each had had a medical examination during the school year, so that it is safe to say that they were in good health when examined

Most of the bloods were drawn between two and three in the afternoon However, no particular effort was made to take bloods always at the same time of day, as this is not done in clinical practice and we wished to determine the full range of normal variation

About one-half the examinations were made in the spring The rest were distributed about equally between the fall and winter months No examinations were made in the summer We do not report the dates since an analysis of our results showed no significant seasonal variations

THE RED CELL COUNT IN NORMAL MALES

The figures for average normal counts (5 million for men and 4.5 million for women) were adopted a long time ago, and have been quoted from one text to another without proper confirmation Few physicians are aware that these figures were based on examination of a small number of bloods Vierordt (1852) and Welcher (1854), each of whom examined the blood of only two persons, are responsible for these figures (according to Bie and Møller⁸)

⁸ Bie, V., and Møller, P. Undersøgelser af normale Menneskers Blod, Ugeskrift for Læger, 1913, pp 749, 817 and 878, Le Sang Humain Normal, Arch de mal du cœur 15 177 (April) 1922

TABLE 2—*Blood Findings in One Hundred and Thirty-seven Normal Young Men*

Subject	Age	Red Cell Count, Millions per Cmm	Hemo- globin, Grams per 100 Cc	Hemoglo- bin per 100 Cc per 5 Million Cells	Color Index	Volume of Cells per 100 Cc	Volume of Cells per 100 Cc per 5 Million	Volume Index	Satu- ration Index
1	21	5.73	14.12	12.32	0.84	43.38	37.86	0.92	0.91
2	25	5.61	14.11	12.57	0.85	40.10	35.75	0.87	0.98
3	24	5.83	14.70	12.60	0.86	42.97	36.85	0.90	0.98
4	29	6.24	16.09	12.89	0.88	49.47	39.65	0.97	0.91
5	29	5.95	15.35	12.90	0.88	44.25	37.18	0.91	0.97
6	22	6.12	16.01	13.06	0.89	45.86	37.41	0.91	0.97
7	25	5.72	14.95	13.06	0.89	39.40	34.56	0.84	1.05
8	27	5.90	15.79	13.08	0.89	45.33	38.42	0.94	0.96
9	24	5.62	14.77	13.14	0.89	45.00	40.03	0.93	0.91
10	25	6.14	16.15	13.15	0.89				
11	19	6.27	16.83	13.18	0.90	45.07	35.94	0.88	1.02
12	22	5.65	15.08	13.35	0.91				
13	21	6.23	16.64	13.36	0.91	50.13	40.24	0.93	0.92
14	23	5.96	16.03	13.44	0.91	45.32	38.02	0.93	0.99
15	23	5.91	15.88	13.44	0.91	44.74	37.85	0.92	0.99
16	20	5.80	15.89	13.44	0.91	45.82	39.50	0.96	0.95
17	22	5.61	15.08	13.46	0.91	45.10	40.26	0.93	0.94
18	25	5.98	16.17	13.52	0.92	43.75	36.58	0.89	1.03
19	24	5.68	15.89	13.54	0.92				
20	26	5.52	14.98	13.56	0.92	42.05	38.09	0.93	0.99
21	24	5.33	14.60	13.70	0.93	44.39	41.64	1.02	0.91
22	21	5.10	14.01	13.73	0.93	41.43	40.62	0.99	0.94
23	25	5.32	14.63	13.75	0.93	44.05	41.40	1.01	0.92
24	26	6.17	17.37	13.76	0.93				
25	26	5.72	15.77	13.78	0.94	43.41	37.95	0.93	1.02
26	24	5.81	16.02	13.79	0.94	47.56	40.93	1.00	0.94
27	24	5.72	15.87	13.87	0.94				
28	30	5.18	14.88	13.88	0.94	41.84	40.39	0.93	0.96
29	25	5.10	14.18	13.90	0.94				
30	22	5.42	15.10	13.93	0.95	44.58	41.13	1.00	0.95
31	27	4.82	13.44	13.94	0.95				
32	26	5.22	14.55	13.96	0.95	38.51	36.88	0.90	1.06
33	25	5.54	15.47	13.96	0.95	42.50	38.37	0.94	1.01
34	24	5.45	15.25	13.99	0.95	44.98	41.27	1.01	0.94
35	27	5.00	13.99	13.99	0.95	41.43	41.43	1.01	0.94
36	24	5.00	14.01	14.01	0.95				
37	29	6.29	17.64	14.02	0.95	48.29	38.38	0.94	1.01
38	22	6.40	18.00	14.06	0.95	50.00	39.05	0.95	1.00
39	23	5.68	15.25	14.06	0.95	44.74	41.24	1.01	0.95
40	23	5.22	14.68	14.06	0.95	46.38	44.43	1.03	0.90
41	22	5.69	16.02	14.08	0.96	48.91	42.98	1.05	0.91
42	28	4.82	13.61	14.11	0.96	41.18	42.71	1.04	0.92
43	23	5.37	15.17	14.12	0.96				
44	30	5.84	16.52	14.14	0.96	48.97	41.93	1.02	0.94
45	25	5.24	14.82	14.14	0.96	41.98	40.05	0.98	0.99
46	22	5.63	15.94	14.16	0.96	47.00	41.74	1.02	0.94
47	22	5.87	16.64	14.17	0.96	46.00	39.18	0.96	1.00
48	22	5.40	15.32	14.18	0.96	45.61	42.23	1.03	0.94
49	24	5.24	14.89	14.21	0.97	45.13	43.06	1.05	0.92
50	22	5.09	14.48	14.22	0.97				
51	25	5.60	15.92	14.22	0.97	46.15	41.20	1.00	0.97
52	28	5.68	16.17	14.24	0.97	47.32	41.66	1.02	0.95
53	27	4.87	14.13	14.25	0.97				
54	20	5.69	16.24	14.27	0.97	49.87	43.82	1.07	0.91
55	23	5.14	14.67	14.27	0.97				
56	21	5.88	16.79	14.28	0.97	48.00	40.82	1.00	0.97
57	24	5.33	15.26	14.32	0.97				
58	22	5.33	15.30	14.33	0.97	44.16	42.31	1.03	0.94
59	23	5.22	14.96	14.33	0.97				
60	25	6.36	18.23	14.33	0.97	45.13	35.48	0.87	1.13
61	24	5.26	15.10	14.36	0.98	43.59	41.45	1.01	0.97
62	24	5.07	14.57	14.36	0.98				
63	25	5.39	15.55	14.41	0.98				
64	27	5.28	15.24	14.43	0.98				
65	24	5.03	14.67	14.44	0.98	42.34	41.67	1.02	0.97
66	24	5.52	16.01	14.50	0.98	45.05	43.52	1.06	0.93
67	28	5.47	15.89	14.52	0.99	46.41	42.43	1.03	0.95
68	20	5.20	15.10	14.52	0.99	45.70	43.94	1.07	0.92
69	27	5.15	14.99	14.55	0.99				
70	26	5.62	16.37	14.56	0.99	47.93	42.65	1.04	0.95

TABLE 2—*Blood Findings in One Hundred and Thirty-Seven Normal Young Men (Continued)*

Subject	Age	Red Cell Count, Millions per Cmm	Hemo- globin, Grams per 100 Cc	Hemoglo- bin per 100 Cc per 5 Million Cells	Color Index	Volume of Cells per 100 Cc	Volume of Cells per 100 Cc per 5 Million	Volume Index	Satu- ration Index
71	25	5.58	16.26	14.57	0.99				
72	24	5.52	16.10	14.59	0.99	45.50	41.31	1.01	0.98
73	27	5.43	15.85	14.60	0.99	46.61	42.91	1.05	0.95
74	21	5.02	14.75	14.69	1.00	36.61	36.17	0.88	1.13
75	28	5.21	15.15	14.71	1.00	44.25	42.96	1.05	0.95
76	23	5.22	15.42	14.75	1.00	40.00	38.31	0.94	1.06
77	25	5.14	15.16	14.75	1.00	43.42	42.24	1.03	0.97
78	23	5.24	15.51	14.80	1.01	45.33	43.25	1.05	0.95
79	21	5.27	15.60	14.80	1.01	41.47	39.35	0.96	1.05
80	25	5.50	16.28	14.80	1.01	40.00	36.36	0.89	1.14
81	23	5.64	16.62	14.84	1.01	43.67	39.90	0.98	1.03
82	26	5.30	15.75	14.85	1.01	45.95	43.35	1.06	0.95
83	22	4.93	14.03	14.89	1.01				
84	24	5.44	16.20	14.89	1.01	48.49	44.56	1.09	0.93
85	24	5.50	16.38	14.89	1.01	47.38	43.08	1.05	0.96
86	24	4.88	14.55	14.90	1.01				
87	22	5.15	15.36	14.91	1.01	46.13	44.79	1.09	0.93
88	27	4.78	14.26	14.92	1.01				
89	23	4.94	14.68	14.92	1.01	41.67	42.17	1.03	0.98
90	27	5.57	16.63	14.93	1.01	48.93	43.55	1.06	0.95
91	21	5.21	15.55	14.93	1.01				
92	27	4.94	14.77	14.95	1.02	45.57	46.13	1.12	0.90
93	22	6.01	17.98	14.96	1.02	45.71	38.02	0.93	1.10
94	21	5.26	15.77	14.99	1.02	45.96	43.68	1.06	0.96
95	24	5.53	16.71	15.11	1.03				
96	22	5.75	17.39	15.12	1.03	45.26	39.44	0.96	1.07
97	21	5.49	16.62	15.13	1.03	46.50	42.35	1.03	1.00
98	28	5.46	16.53	15.14	1.03	46.69	42.75	1.04	0.99
99	30	5.99	18.18	15.17	1.03	47.48	39.63	0.97	1.07
100	27	5.16	15.66	15.18	1.03				
101	27	5.99	18.63	15.20	1.04	47.79	39.90	0.97	1.08
102	23	5.16	15.83	15.24	1.04				
103	24	5.03	15.50	15.25	1.04				
104	25	5.17	15.79	15.27	1.04	36.09	34.91	0.86	1.21
105	25	5.53	16.93	15.31	1.04	46.68	42.21	1.03	1.01
106	29	5.24	16.09	15.35	1.04				
107	25	5.10	15.66	15.35	1.04				
108	24	5.28	16.25	15.39	1.05	45.20	42.81	1.04	1.01
109	29	5.74	17.65	15.39	1.05	49.17	42.83	1.04	1.01
110	27	5.54	17.07	15.41	1.05	46.78	42.22	1.03	1.02
111	29	4.99	15.46	15.49	1.05	43.00	43.09	1.05	1.00
112	22	5.71	17.72	15.52	1.05	48.16	42.17	1.03	1.02
113	23	5.88	18.33	15.59	1.06	48.10	40.90	1.00	1.06
114	23	5.08	17.75	15.62	1.06	47.01	41.38	1.01	1.05
115	24	5.08	15.87	15.62	1.06	43.38	42.69	1.04	1.02
116	22	5.14	16.06	15.63	1.06	40.52	39.41	0.96	1.11
117	20	5.60	17.53	15.65	1.06	47.00	41.96	1.02	1.04
118	24	5.16	16.22	15.71	1.07	44.97	43.59	1.06	1.01
119	23	4.46	14.04	15.72	1.07	40.82	45.72	1.12	0.96
120	25	4.70	14.80	15.77	1.07	41.28	43.92	1.07	1.00
121	28	4.81	15.36	15.96	1.08				
122	28	4.83	15.44	15.99	1.09				
123	25	4.84	15.49	16.00	1.09				
124	22	5.12	16.50	16.09	1.09				
125	27	4.91	15.84	16.11	1.11				
126	22	5.31	17.40	16.38	1.12	40.00	37.67	0.92	1.21
127	25	4.78	15.66	16.38	1.12	40.57	41.91	1.02	1.09
128	25	4.73	15.55	16.44	1.12				
129	26	4.92	16.23	16.49	1.12				
130	23	5.74	19.03	16.58	1.13	51.87	45.19	1.10	1.02
131	24	5.31	17.66	16.63	1.13				
132	28	4.70	15.65	16.65	1.13				
133	24	4.49	14.95	16.65	1.13				
134	27	4.85	16.26	16.75	1.14				
135	25	4.57	15.97	17.47	1.19				
136	26	4.41	15.66	17.76	1.21				
137	27	4.83	17.25	17.85	1.21				
Average		5.39	15.76	14.66	1.00	44.84	40.80	1.00	1.00

A survey of the literature to date (September, 1925) shows that reasonably accurate red cell counts have been reported for only thirty-one normal males between the ages of 19 and 30 (the age limits for our work reported in this paper) distributed as follows

Bierring⁹ 4 men, averaging 5.05 million
 Gram and Norgaard¹⁰ 7 men, averaging 5.40 million
 Haden¹¹ 20 men, averaging 5.08 million
 Total 31 men, averaging 5.15 million

These are the only counts that can properly be compared with our own. The average count on our 137 men was 5.39 million.¹² Our counts ranged from 4.4 to 6.4 million, while in the thirty-one counts cited above the range was from 4.52 to 5.91 million.

Aside from the work reported above, presumably accurate counts on 153 men are given in the literature, without any statement as to ages. They are distributed as follows

Capps¹³ 4 men, averaging 5.15 million
 Bock¹⁴ 4 men, averaging 4.95 million
 Bie and Møller⁸ 10 men, averaging 5.53 million
 Larrabee¹⁵ 13 men, averaging 5.33 million
 Bing¹⁶ 19 men, averaging 5.50 million
 Gram¹⁷ 32 men, averaging 5.37 million
 Ten other authors¹⁸ 71 men, averaging 5.39 million
 Total¹⁹ 153 men, averaging 5.38 million

9 Bierring, K. Svingninger i Erythrocyttallet hos normale Mennesker, *Ugeskr. f. Læger* **82** 1445 (Nov. 18) 1920.

10 Gram, H. C., and Norgaard, A. Relation Between Hemoglobin, Cell Count and Cell Volume in the Venous Blood of Normal Human Subjects, *Arch. Int. Med.* **31** 164 (Feb.) 1923.

11 Haden, R. L. The Normal Hemoglobin Standard, *J. A. M. A.* **79** 1496 (Oct. 28) 1922, Accurate Criteria for Differentiating Anemias, *Arch. Int. Med.* **31** 766 (May) 1923.

12 Reference should be made to table 2 for our detailed results.

13 Capps, J. A. A Study of the Volume Index, *J. M. Res.* **10** 367 (Dec.) 1903.

14 Bock, A. V. The Constancy of the Volume of the Blood Plasma, *Arch. Int. Med.* **27** 83 (Jan.) 1921.

15 Larrabee, R. C. The Volume Index of the Red Corpuscles, *J. M. Res.* **24** 15 (Jan.) 1911.

16 Bing, H. I. On the Number of Red Blood Corpuscles at Different Ages and Under Different Circumstances, *Proc. Ninth Northern Congress Int. Med., Acta med. Scandinav.* **53** 833, 1921.

17 Gram, H. C. Om det normale Erythrocyttale og den normale Hemoglobinmængde i Venøblod, *Ugeskr. f. Læger* **82** 1543 (Dec. 9) 1920, On the Standardization of Hemoglobinometers and Its Importance for Index Calculation, *Acta med. Scandinav.* **57** 27 (Nov.) 1922.

18 Writers quoted by Bie and Møller (Footnote 8).

19 The average of 4.92 million obtained by E. Meyer and E. E. Butterfield (The Color Index of the Red Corpuscles, *Arch. Int. Med.* **14** 94 [July] 1914) on seven men (ages not reported) is not included because they used defibrinated blood. It is obviously impossible to defibrinate blood without changing the red cell count.

The close agreement of this general average with our average (5.39 million) may be accounted for if, as is probable, these investigators examined the blood of college students (men of the same age limits as ours). The counts on the 153 men ranged from 4.2 to 6.39 million (ours ranged from 4.4 to 6.4 million).

It is fully as important, however, to know the range of the most frequently occurring normal red cell counts as to know the extreme limits. Frequency figure 2 shows the distribution of our 137 counts. From it we see that counts at any point between 4.9 and 5.9 million are common, while about 90 per cent of them fall between 4.7 and 6.1 million cells.

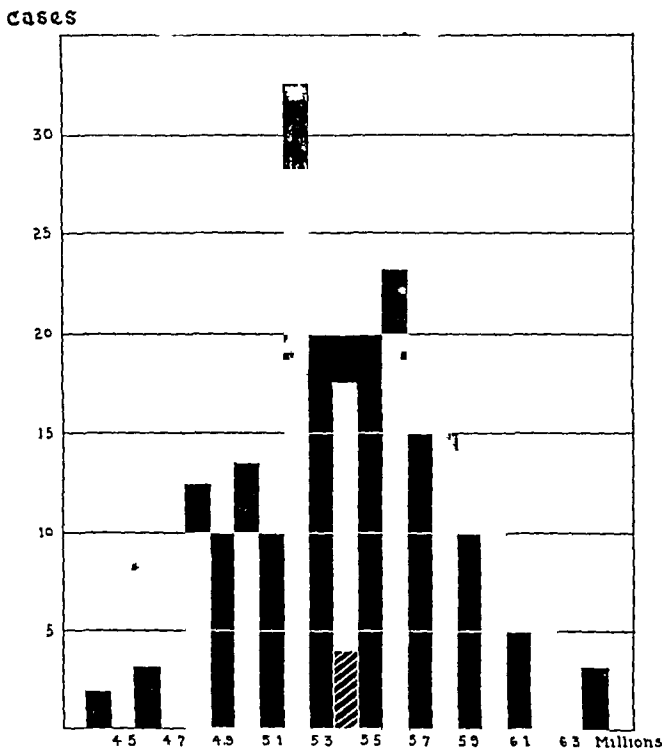


Fig 2—Red cell counts in one hundred and thirty-seven healthy young men

The tendency to a double peak in the chart probably is not significant. If a large enough number of men were examined the most frequently occurring, as well as the average, figure would undoubtedly be about 5.4 million. The average is indicated in the chart (similarly also in figures 3 to 7) by a column having oblique lines in the lower portion. It will also be noticed that counts between 4.4 and 4.7 million and between 6.1 and 6.4 million do occur occasionally in normal men. Yet textbooks still state that a red cell count of 6 million or more justifies a diagnosis of polycythemia.

HEMOGLOBIN CONTENT OF THE BLOOD IN NORMAL MALES

The literature on normal hemoglobin standards is difficult to summarize because so many different methods of hemoglobin estimation have

been used, few of which are sufficiently accurate for research purposes. Thus, we have found in the literature reliable hemoglobin estimations reported for only seventy males between 19 and 30 years of age. The average grams of hemoglobin per hundred cubic centimeters of blood for each group of cases follows:

Brown²⁰ and Rowntree² (Palmer's method, checked by Osgood-Haskins' method)
7 men, averaging 16.27 Gm
Gram and Norgaard¹⁰ (Autenrieth-Konigsburger colorimeter method) 7 men,
averaging 14.83 Gm
Haden¹¹ (Van Slyke's method) 20 men, averaging 15.83 Gm
Williamson²¹ (spectrophotometer) 36 men, averaging 16.80 Gm
Total 70 men, averaging 16.27 Gm

This average is not widely different from our average of 15.76 Gm for 137 men. If we figure in our results, the average for the total 207 men is 15.93 Gm. This figure is much higher than the 13.8 Gm quoted in most texts. The wide variations in the averages reported by different authors, as shown in the preceding paragraph, is probably due to the small number of men examined. The extremes in thirty-four²² of the seventy examinations are 13.30 and 19.46 Gm. Our extremes on 137 men are 13.44 and 19.03 Gm.

Beside the foregoing cases (which are the only ones comparable to our own) we have found the following reports of accurate estimations on thirteen adult males, the ages not being given:

Bock¹⁴ (Van Slykes method) 3 men, averaging 17.0 Gm
Lundsgaard²³ (Palmer's method) 10 men, averaging 14.7 Gm
Total 13 men, averaging 15.23 Gm

For the sake of completeness we include the following reports of examinations of 132 men by obsolete or unsatisfactorily standardized methods:

Bie and Moller⁸ (Meisling colorimeter) 10 men, averaging 14.80 Gm
Haldane²⁴ (Haldane oxygen capacity method)²⁵ 12 men, averaging 13.80 Gm
Haldane and Smith²⁶ (Haldane's method) 12 men, averaging 13.80 Gm.
Bing¹⁶ (Sahl's method) 19 men, averaging 15.46 Gm

20 Brown, G. E. Personal communication to the author on age and sex.

21 Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch. Int. Med.* **18**: 505 (Oct.) 1916.

22 Williamson (footnote 21) did not report his extremes.

23 Lundsgaard, C. Studies of Oxygen in the Venous Blood, *J. Biol. Chem.* **33**: 133 (Jan.) 1918.

24 Haldane, J. The Colorimetric Determination of Hemoglobin, *J. Physiol.* **26**: 497 (June) 1901.

25 All of Leichtenstern's and six of Haldane's patients were between 19 and 30 years of age. No statement is made about age by the other authors.

26 Haldane, J., and Smith, J. L. The Mass and Oxygen Capacity of the Blood in Man, *J. Physiol.* **25**: 331 (Aug.) 1900.

Leichtenstern²⁷ (spectrophotometer²⁸) 22 men, averaging 14.40 Gm²³
 De Jong²⁹ (Sahli method) 25 men, averaging 12.63 Gm
 Gram³¹ (Autenrieth Hellige colorimeter) 32 men, averaging 13.66 Gm
 Total 132 men, averaging 13.96 Gm

Results as low as 11.7 Gm and as high as 17 Gm are included in the foregoing

The 13.8 Gm figure given in many texts is based on the few estimations reported by Haldane,²⁴ made by a method that is now obsolete. He reported no red cell counts, so that even supposing his hemoglobin

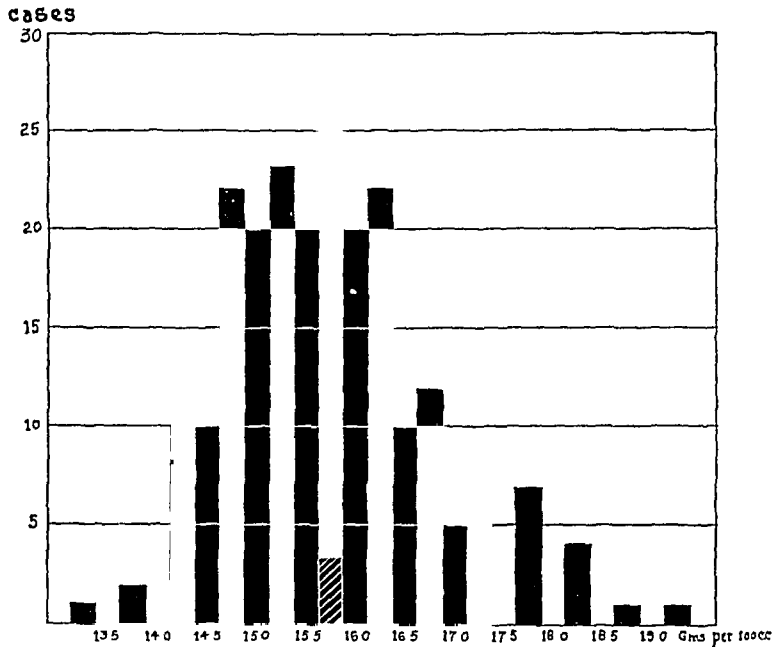


Fig 3—Total hemoglobin in one hundred and thirty-seven men

determinations were correct, the use of 13.8 Gm of hemoglobin per hundred cubic centimeters as 100 per cent in computing color indexes has never been justified

As the hemoglobin estimations reported by Laache,³⁰ Capps,¹⁸ Meyer and Butterfield,¹⁹ Rosedale³¹ and Emerson³² were too inaccurate to be of value, they are omitted

27 Leichtenstern, O Untersuchungen über den Haemoglobingehalt des Blutes in gesunden und kranken Zuständen, Leipzig, 1878

28 Sahli (Diagnostic Methods, 1911, p 743) is authority for the basis of calculation of this figure from Leichtenstern's data

29 De Jong, J J Le Taux de le Hemoglobine du Sang et le Volume des Globules Rouges par Rapport a la Signification de la Valeure Globulaire, Presse méd 32 789 (Oct 1) 1924

30 Laache, S Die Anamie, Christiania, 1883

31 Rosedale, G Observations with the Hematocrit Volume-Color Index, Quart J Med 16 245 (April) 1923

32 Emerson, C P Clinical Diagnosis, ed 5, Philadelphia, J B Lippincott Company, 1921, p 44

Our average of 15.76 Gm of hemoglobin per hundred cubic centimeters of blood is also the most frequently occurring figure (fig 3). Over 90 per cent of the estimations are between 14 and 18 Gm.

COLOR INDEX

The essentials for a color index determination that will be of value in diagnosis are

- 1 An accurate red cell count on the patient's blood
- 2 An accurate hemoglobin estimation on the same blood

3 A normal standard for comparison. This standard is the average number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a count of 5 million red cells per cubic millimeter in the average healthy person of the same age and sex. We suggest the term *hemoglobin coefficient* to replace the cumbersome expression "the number of grams of hemoglobin per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter." We use it hereafter with this meaning. The color index is calculated by dividing the percentage of hemoglobin by the percentage of red cells. For this calculation the normal hemoglobin coefficient (for the patient's age and sex) is considered as 100 per cent, and a red cell count of 5 million is considered as 100 per cent.

Previous to our work the normal hemoglobin coefficient has never been satisfactorily determined for any sex or age group. Enough data has been accumulated, however, to show that it probably does vary with age and sex, and that neither 13.8 Gm nor 16.92 Gm (100 per cent hemoglobin equivalents on the reading scales of two commonly used hemoglobinometers) is anywhere near the correct figure for adult males. Therefore it is necessary to convert all hemoglobin estimations into terms of grams per hundred cubic centimeters before calculating color indexes, and it would be desirable to have all hemoglobinometers standardized to read in grams per hundred cubic centimeters. Until this has been brought about each clinician should find out the number of grams of hemoglobin equivalent to 100 per cent on his hemoglobinometer, and then convert his results into grams per hundred cubic centimeters.

Many physicians do not seem to be aware that the most commonly used methods of hemoglobin estimation are not sufficiently accurate for color index work. Other workers³³ agree with our observations that the Dare and Tallquist methods (13.8 Gm per hundred cubic centimeters taken as 100 per cent) frequently give results varying from accurate estimations by as much as 20 per cent, and we have found errors as great

33 Senty, E. G. A Comparative Study of Various Methods of Hemoglobin Determinations, *J. Lab. & Clin. Med.* 8:5 (June) 1923. Brown, G. E. Prognostic Value of Anemia in Chronic Glomerular Nephritis (chart 1), *J. A. M. A.* 81:1949 (Dec. 8) 1923.

as 12 per cent in the estimations made by the new Bausch and Lomb Newcomer hemoglobinometer (16.92 Gm per hundred cubic centimeters equalling 100 per cent)

We were unable to find any satisfactory data for calculating normal hemoglobin coefficients for males between 19 and 30 years of age at the time our work was started. Recently, however, results have been reported on twenty-seven men. There is a marked difference between the hemoglobin coefficient (13.73 Gm) reported by Gram and Norgaard¹⁰ on seven men, and the hemoglobin coefficient (15.57 Gm) reported by Haden¹¹ on twenty men. This difference probably is due to the small number of cases examined, as all the results fall well within

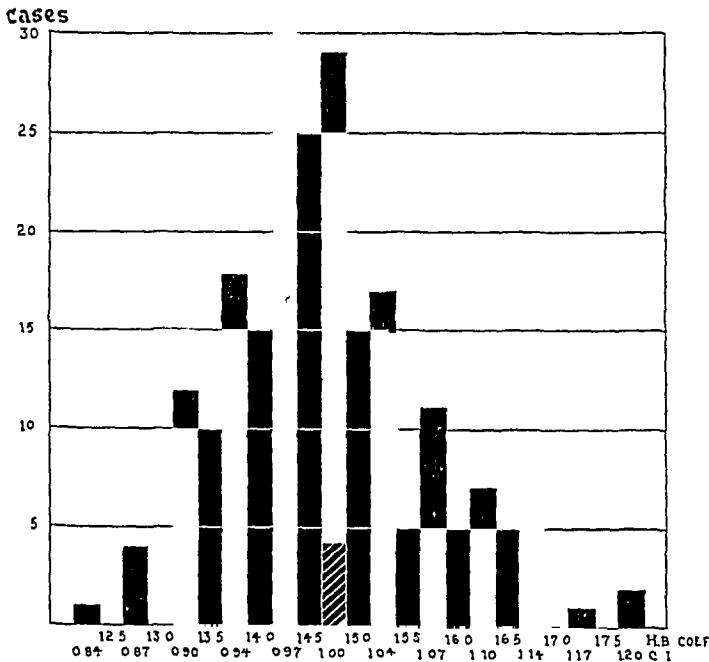


Fig 4—Hemoglobin coefficients and color indexes in one hundred and thirty-seven men

the normal limits of variation determined by us. It may, however, be a national or racial difference, as Gram and Norgaard presumably worked in Denmark and Haden in Kansas City. The average for the twenty-seven men is 15.09 Gm, with extremes of 13.47 and 16.7 Gm.

Our average (on 137 men) of 14.66 Gm is somewhat less than the average on the twenty-seven men. The average for all the cases (164 men) is 14.73 Gm. Our extremes extend above and below those found in the case of the twenty-seven men examined by others, as might be expected with the larger series of cases. In frequency figure 4 it should be noted that there is a tendency to form a peak in the region of the average, and also that about 90 per cent of the hemoglobin coefficients are between 13 and 16.5, corresponding to color indexes between 0.9 and 1.1. We should expect, therefore, that almost all normal

males between 19 and 30 years of age will yield a color index of from 0.9 to 1.1 on the basis of the normal hemoglobin coefficient determined by us for this sex and age group, i. e., 14.7 Gm

TOTAL CELL VOLUME

Before comparing the results of different workers, it is necessary to study their methods. These may be divided into three groups, as follows

- 1 Methods in which the plasma is not diluted and remains isotonic
 - (a) Heparin
 - (b) Hirudin
- 2 Methods in which the plasma is diluted but remains isotonic
 - (a) Three per cent sodium citrate, 1 part added to 9 parts of blood
 - (b) One and six-tenths per cent sodium oxalate, 1 part added to 10 parts of blood
- 3 Methods in which the plasma is not diluted but becomes slightly hypertonic
 - (a) Potassium oxalate, 20 mg per ten cubic centimeters of blood
 - (b) Sodium oxalate, 16 mg per ten cubic centimeters of blood

The methods in group 1 are theoretically ideal, but the expense of the hirudin or heparin makes these methods clinically impracticable. The methods in group 2 give satisfactory results, but the blood used for cell volume determination is unsuitable for counts or hemoglobin estimation. The rapidity with which untreated blood must be measured to avoid clotting before mixing with the anticoagulant is apt to lead to inaccuracies. With the methods in group 3 the possibility of shrinkage of the cells must be considered. To determine this point two types of experiments were employed. In the first type portions of well mixed, defibrinated blood were treated as in the methods of groups 2 and 3 with 3 per cent sodium citrate, 1.6 per cent sodium oxalate, and powdered potassium oxalate. As a control another portion was treated with 0.86 per cent sodium chloride in the proportion of 2 parts of saline solution to 10 parts of blood. After fifteen minutes exposure the four samples were centrifugated and freezing point determinations were made in triplicate on each serum. The serums from the bloods treated with sodium citrate, sodium oxalate and sodium chloride solutions all gave a depression of the freezing point of 0.572 degrees. The serum from the blood treated with potassium oxalate crystals gave a depression of 0.654 degrees. The 20 mg of potassium oxalate increased the osmotic pressure to the same extent that the addition of 13.6 mg of sodium chloride would have done. In the second type of experiment 30 cc of human blood was prevented from clotting by mixing with 6 mg of heparin. Portions of this blood were then treated with

sodium citrate and sodium oxalate solutions, and with powdered potassium oxalate as described in the foregoing. A fourth portion containing only the heparin served as control. These portions were then centrifugated simultaneously to constant volume. The results expressed as cubic centimeters of cells per hundred cubic centimeters of blood in two such experiments follow

Results by methods of groups 1a, 2a and 2b ³⁴	30 66 cc	44 50 cc
Results using potassium oxalate crystals (group 3)	29 55 cc	43 00 cc
Difference	1 11 cc	1 50 cc

The difference in volume due to shrinkage is in the first instance 3.6 per cent and in the second instance 3.4 per cent of the volume of unchanged packed cells. This shrinkage is not enough to alter the clinical significance of the volume index figures, even if they were calculated on the basis of a standard volume determined by the methods of groups 1 or 2. As the shrinkage is constant (about 3.5 per cent), if the volume index calculation is based on standards determined by our potassium oxalate method the indexes will be absolutely correct. Since this method is cheaper than those of group 1 and quicker than those of group 2, but just as accurate as the other methods (more accurate if centrifugating to constant volume is disregarded by those using the other methods) it is preferable for clinical use.

Brown and Rowntree,² also Keith³⁵ and his co-workers used methods somewhat similar to our own, but with uncertainty as to the adequacy of the centrifugating. Their results on the sixteen men between 19 and 30 whom they examined average 43.7 cc of cells per hundred cubic centimeters of blood. No red cell counts were reported. Gram³⁶ reports twenty-five volume determinations on men, using 3 per cent citrate and centrifugating one and one-half hours at 3,000 revolutions per minute. As he did not give red cell counts, his high average (48 cc of cells per hundred cubic centimeters of blood) can be explained only by a high average count. Ages were not mentioned. Haden¹¹ examined twenty men between 19 and 30 years of age. He reports red cell counts. He used 1.6 per cent sodium oxalate. However, since he centrifugated only thirty minutes at 2,500 revolutions per minute the cell volumes of some of his bloods are too high. Therefore, his average volume (46.5 cc) is too high. The only results by others that seem to be above criticism and that can be fairly compared with our results are those of Gram and Norgaard¹⁰ (hirudin method, centrifugating for one and

34 The dilution with sodium oxalate or sodium citrate solutions did not diminish the time required for complete packing.

35 Keith, N. M., Rowntree, L. G., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch Int Med* **16**:547 (Oct) 1915.

36 Gram, H. C. A New Method for the Determination of the Fibrin Percentage in Blood and Plasma, *J Biol Chem* **49**:279 (Dec) 1921.

one-half hour at 3,000 revolutions per minute) on seven men between 19 and 30. Their average volume was 45.9 cc. The average for our ninety-four men (corrected for the 3.5 per cent shrinkage) is 46.4 cc, a good agreement. The average of the observed volumes on our ninety-four men was 44.84 cc. If Gram and Norgaard's results are brought to the same basis as our results by deducting 3.5 per cent, their average volume becomes 44.3 cc. Further, if their cases are included with our cases, the average for 101 men of this age group becomes 44.8 cc.

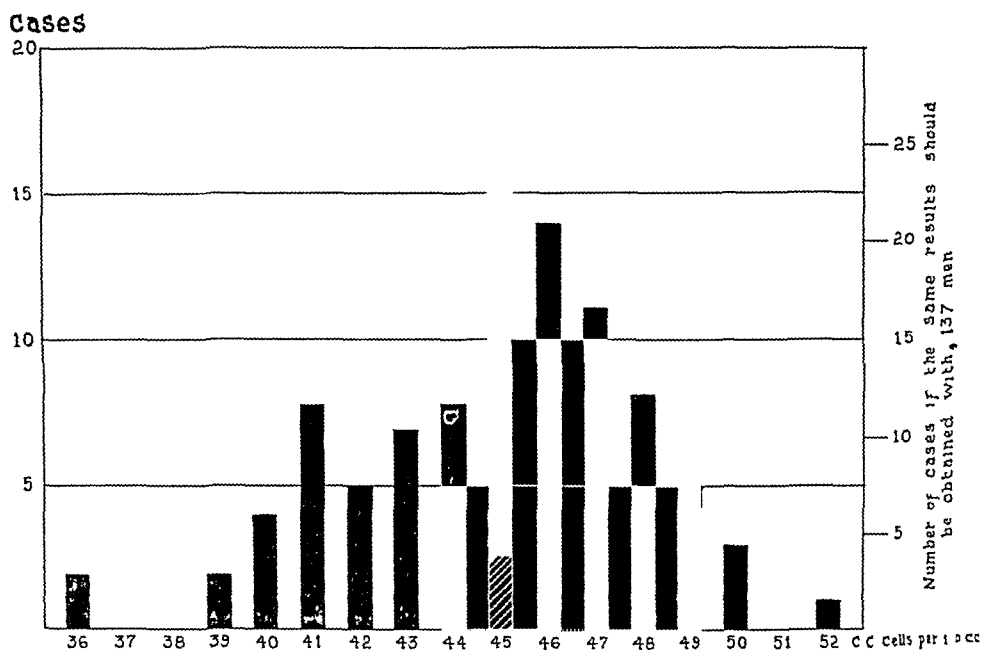


Fig 5—Total volume of cells in ninety-four men

Therefore, we recommend that 45 cc be considered as the average normal volume of packed cells per hundred cubic centimeters of blood (without reference to the red cell count) when our method is used. Frequency figure 5 shows that there is a definite peak in the region of this average, and that over 90 per cent of the results are between 40 and 50 cc.

VOLUME INDEX

The volume index of a particular blood expresses the ratio between the average size of the red cells in that blood and the average size of the red cells in the blood of healthy persons of the same sex and in the same age group. This index is determined by dividing the volume of the cells expressed as percentage of the average normal volume (100 per cent being considered as the average volume of cells in 100 cc of blood calculated to a red cell count of 5 million, found in healthy persons of the same sex and age group) by the percentage of red cells (5 million being 100 per cent). We suggest the term *volume coefficient* as a substitute for the awkward expression "volume of packed red cells per hundred

cubic centimeters of blood calculated to a red cell count of 5 million" We use it hereafter with this meaning

The value of the volume index determination in the differential diagnosis of anemias was first pointed out by Capps¹³ and has been emphasized recently by Haden¹¹ Volume index determinations cannot be satisfactory for clinical purposes until a good and uniform technic for cell volume estimation has been adopted by all workers Also, the normal volume coefficients for each sex in the various age groups should be established as soon as possible

The volume coefficients calculated from our data (ninety-four men between 19 and 30 years of age) average 40.8, varying from 34.5 to 46 These extremes correspond to volume indexes of from 0.86 to 1.12 Gram and Norgaard¹⁰ report the only satisfactory volume coefficients

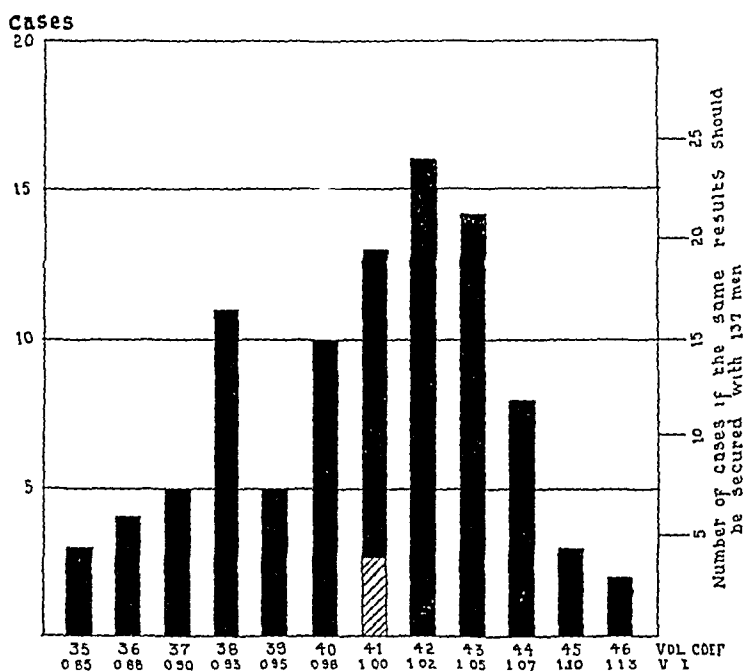


Fig 6—Volume coefficients and volume indexes in ninety-four men

we were able to find in the literature, but they examined only seven men in this age group If 3.5 per cent is deducted from their average to make their results comparable to ours, their figure, 41, agrees very well with ours, 40.8 We also mention Haden's¹¹ results on twenty men (from 18 to 30 years of age), although we believe his average, 45.92, is too high He neglected to centrifugate to constant volume, and our experience has shown that his thirty minute period of centrifugating at 2,500 revolutions per minute is not sufficient to pack the cells of many normal bloods completely Sedimentation times of normal bloods vary markedly, and some are high Therefore, if actual cell volume is to be determined we cannot overemphasize the importance of centrifugating to constant volume

The average volume coefficient for 101 men (excluding Haden's results) is 40.8. Therefore, we make the tentative recommendation that 41.0 be used as the normal volume coefficient for men between 19 and 30 years of age when our technic is used. The frequency distribution of volume coefficients and of the volume indexes of the blood of our ninety-four men is shown in figure 6. The volume indexes are calculated on the basis of a volume coefficient of 41 as 100 per cent. It will be seen that over 90 per cent of the volume coefficients fall between 37 and 45, that is, between volume indexes of 0.9 and 1.1.

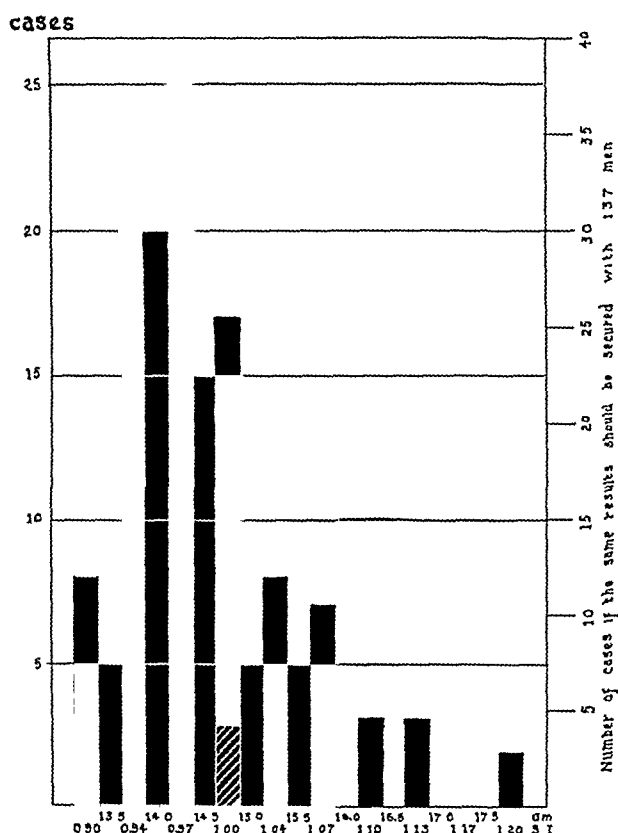


Fig. 7—Grams of hemoglobin per 41 cc of cells and saturation indexes in ninety-four men

SATURATION INDEX

Haden¹¹ coined the term saturation index for the figure expressing the ratio between the concentration of hemoglobin per unit volume of cells in a particular subject and the average concentration of hemoglobin per unit volume of cells in normal subjects of the same sex and age group. It is most easily calculated by dividing the color index by the volume index.

Sufficient data for calculation of saturation indexes are reported by Gram and Noirgaard¹⁰ for seven men and by Haden¹¹ for twenty men.

Their results are not comparable with ours because their technic for cell volume determination differs from ours

In figure 7 are plotted the grams of hemoglobin per 41 cc of packed cells in the blood of our ninety-four men. It will be noticed that there is a tendency to form a peak in the region of the average (14.6 Gm),³⁷ and that over 90 per cent of the results fall between 13 and 16.5 Gm, corresponding to saturation indexes of 0.9 to 1.1

FURTHER STUDIES SUGGESTED

Our work has suggested so many lines of investigation that are made possible by the methods we have used that it seems best to outline some of the more important

1. What are the normal hemoglobin, color index and volume index standards for other age groups of both sexes? We have made a start toward duplicating our investigations by work on women between 19 and 30 years of age. We hope to report this in the near future. The literature is meager and unsatisfactory for other age groups. Practically no work has been done on volume index or saturation index determinations in children. These problems simply require repetition of the technic described here. Obviously the results of such investigations are certain to be of value.

2. Are there racial or geographical differences (aside from altitude) in these blood findings? In our German and Scandinavian students we have noted a tendency toward a red cell count in the higher ranges, with a volume index and color index in the lower ranges of the normal. This would indicate red cells of small size. The number of these men in our series was too small to be of any statistical value, however. If such a tendency does exist, it would account for the low hemoglobin coefficients that continue to be reported from those countries. Our results also require confirmation by work on those living in other parts of the United States and Canada.

3. Is there a marked diurnal variation in the hemoglobin content of the blood of normal persons as claimed by Dreyer,³⁸ Ward³⁹ and Rabinowitch?⁴⁰ If so, is this accompanied by corresponding changes in red cell count and cell volume? More complete examinations checked with control estimations to show the limits of error in the technic are

37 This figure agrees well with the hemoglobin coefficient (14.66 Gm) found in the group of 137 men. The figures would, of course, be identical if they were derived from exactly the same series of cases.

38 Dreyer, G., Bazeth, H. C., and Pierce, H. F. Diurnal Variations in the Hemoglobin Content of the Blood, *Lancet* **199** 588 (Sept. 18) 1920.

39 Ward, H. C. The Hourly Variations in the Quantity of Hemoglobin and in the Number of the Corpuscles in Human Blood, *Am. J. Physiol.* **11** 394 (July) 1904.

40 Rabinowitch, I. M. *J. Lab. & Clin. Med.* **9** 120 (Nov.) 1923.

needed to confirm these reports. The hemoglobin estimations reported by Rabinowitch³⁹ are too low to be comparable to our results. If such variations do occur it may be advisable to draw the blood before breakfast as is done for blood chemistry work.

4 Is there a seasonal variation in the hemoglobin content and in the number of erythrocytes of blood as is asserted in some texts? The fact that we found no significant seasonal variations in our group is not sufficient evidence. Daily complete blood studies should first be made on a group of normal persons to determine the amount of variation to be expected within one season. Then, throughout the year, weekly or biweekly examinations should be made on the bloods of the same persons. The climatic conditions should be studied in connection with this work. The blood for these examinations should preferably be taken at the same hour before breakfast.

TABLE 3—*Classes of Anemia*

	Group	Color Index	Volume Index	Saturation Index	Possible Diagnostic Significance
Volume index and color index vary in proportion to one another (saturation index normal)		From 0.85 to 1.15	From 0.85 to 1.15	From 0.85 to 1.15	Normals
	1	Less than 0.85	Less than 0.85	From 0.85 to 1.15	Hemolytic type of secondary anemia
	2	More than 1.15	More than 1.15	From 0.85 to 1.15	Uncomplicated pernicious anemia
	3	From 0.85 to 1.15	From 0.85 to 1.15	From 0.85 to 1.15	Aplastic anemia and anemia of acute blood loss
Volume index higher than color index (saturation index low)	4	Less than 0.85	Somewhat less than 0.85	Less than 0.85	Anemia of chronic blood loss
	5	Less than 1.15	More than 1.15	Less than 0.85	Pernicious, with coexisting secondary anemia
	6	Less than 0.85	From 0.85 to 1.15	Less than 0.85	Chlorosis and chlorotic type secondary anemia
Volume index lower than color index (saturation index high) (probably does not occur)	7	From 0.85 to 1.15	Less than 0.85	More than 1.15	Obsolete views of the blood findings in pernicious anemia
	8	More than 1.15	From 0.85 to 1.15	More than 1.15	
	9	More than 1.15	Somewhat more than 1.15	More than 1.15	

5 May it not be possible for diagnostic purposes to subdivide anemias according to their color indexes, volume indexes and saturation indexes? No work on the clinical value of the saturation index has been reported. A little work has been done on volume index which, if confirmed, makes a high volume index the most valuable single laboratory finding in the diagnosis of pernicious anemia. We have, as yet, made a thorough study of only sixty-three cases of anemia. In fifteen of these cases the volume index was high and the diagnosis of pernicious anemia was established. Two other cases showed high volume indexes, but the diagnosis of pernicious anemia has not yet been made by the clinician, both of these must be followed for a longer time.

Nine classes of blood disorders are theoretically possible (table 3). We suggest this tentative classification only as a working basis for group-

ing large numbers of carefully studied cases of anemia Groups 7, 8 and 9 probably do not occur, although this has not been adequately proved Of the other groups, we have studied no cases in group 6 (this group probably occurs) and only one case in group 1 Our experience with the other sixty-two cases of anemia leads us to believe that we have attributed the proper diagnostic significance to the findings in groups 2, 3, 4 and 5 We hope that the diagnostic significance of this classification will be confirmed or amended in the near future

TABLE 4—*Averages and Range of Variation in Normal Findings in One Hundred Thirty-Seven Men*⁴¹

	Average	Range of Results
Red cell count	5.4	90 per cent, from 4.7 to 6.1 million per cubic millimeter
Total hemoglobin	15.8	90 per cent, from 14 to 18 gm per hundred cubic centimeters
Hemoglobin coefficient	14.7	
Color indexes	1.0	90 per cent, from 0.9 to 1.1
Total volume of cells	45.0	90 per cent, from 40 to 50 cc per hundred cubic centimeters
Volume coefficient	41.0	
Volume indexes	1.0	90 per cent, from 0.9 to 1.1
Saturation indexes	1.0	90 per cent, from 0.9 to 1.1

SUMMARY

1 The bloods of 137 men from 19 to 30 years of age have been studied for the purpose of establishing standards for the normal averages and determining the range of variation in normal findings (table 4) A review of the literature covering the same points for normal men of the same age group is presented

2 The term *hemoglobin coefficient* is proposed as a substitute for "the amount of hemoglobin in grams per hundred cubic centimeters of blood calculated to a red cell count of 5 million per cubic millimeter" This is the figure used as 100 per cent hemoglobin in calculating color indexes

3 Similarly, the term *volume coefficient* is proposed to take the place of "the volume of packed red cells in cubic centimeters in 100 cc of blood calculated to a red cell count of 5 million per cubic millimeter" This is the figure used as 100 per cent cell volume in calculating volume indexes

4 The term saturation index was proposed by Haden to express the ratio between the average hemoglobin content per unit volume of cells in the blood examined and the average hemoglobin content per unit volume of cells in the blood of normal persons of the same sex in the same age group Our method of calculating saturation indexes by dividing the color index by the volume index is simpler than Haden's method of calculation

⁴¹ The altitude at the place of estimation is not over 500 feet

5 Figures 2 to 7 have been so constructed that one may see at a glance the frequency distribution and the extremes for each type of finding

6 The methods employed are practical for clinical as well as research use Our method of centrifugating to constant volume simplifies and increases the accuracy of volume index determinations

7 The hematocrit is not a reliable substitute for hemoglobin estimations or for red cell counts

8 The use of oxalated venous blood (20 mg of powdered potassium oxalate per 10 cc) is advised for all work, including red cell counts

9 A tentative classification of anemias on the basis of color index, volume index and saturation index is suggested

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ESTIMATION OF TRANSVERSE CARDIAC DIAMETER IN MAN *

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In recent years the employment of roentgenologic methods has been advocated by numerous writers as a means of developing greater accuracy in the field of cardiac diagnosis. Notable among these have been Vaquez and Bordet¹ and their co-workers in France, who have been largely responsible for the perfection of the orthodiascopic technic which has been so successful in their hands.

Various measurements of the cardiac silhouette as obtained by teleoroentgenographic or orthodiagraphic methods have been proposed, but in more recent times, following the work of Bardeen,² these have usually been restricted to two, the area of the silhouette and its greatest transverse diameter. Cardiac area as determined by the planimeter measurement of the orthodiagraphic or teleoroentgenographic tracings is a measurement that can be made with surprising accuracy despite the fact that several writers have expressed doubt as to the ability of even the most experienced observer accurately to complete the more or less arbitrary upper and lower heart borders.

In the hands of one with experience in this work, the results from the same subject on different occasions check closely³ and different observers using the same tracings usually obtain variations of only a few square centimeters in area. The orthodiagraphic method increases the accuracy of area measurements by giving somewhat more of the cardiac border than it is possible to obtain from films. In the determination of exact transverse diameter measurements from cardiac shadows, however obtained, the points between which the distance is taken are always to be found on the unobstructed cardiac contours, thereby reducing the personal factor to a negligible minimum. The fact that a heart of a given size will show a narrow transverse diameter if suspended more or less freely in a long chest, or a wide diameter if pushed upward into a transverse position by an elevated diaphragm cannot so easily be accepted as compatible with the use of this measurement as a valuable index of cardiac normality or pathology. If one were able to show, however, that transverse cardiac diameter in individuals free from

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1 Vaquez, H., and Bordet, E. *The Heart and the Aorta*, translated from the French by Honeij and Macy, Yale University Press, 1920.

2 Bardeen, C. R. *Determination of the Size of the Heart by Means of the X-Rays*, *Am J Anat* 23 423-487 (March) 1918.

3 Eyster, J. A. E., and Evans, J. S. *Tr A Am Phys*, 1923.

cardiac disease of any sort bears a constant relationship to one or more body measurements which can be readily and accurately obtained, this relationship could be advantageously used to predict in which individuals the heart may be expected to lie transversely and in which vertically, or, in other words, to predict with some accuracy the most probable diameter in any given individual. The existence and extent of such relationship can be determined by the method of statistical analysis known as the correlation of a criterion (in this case transverse diameter of the normal heart) with one or more variables (such as height and weight).

Laborious as we beginners in this field of analysis find the required mathematical procedures so widely used by the medical psychologists, the results of such endeavor are well worth the effort, for such a study of otherwise abstruse data permits of their accurate and positive interpretation. For instance, at first thought one might be so impressed by the effect of diaphragm level in determining cardiac position as to suppose that in tall persons with long chests one will find a predominance of narrow diameters. In this assumption he will be partially correct, but by analyzing a group of normal cases by the method suggested, we can say with certainty that the inverse relationship of height to transverse diameter is slight as compared to the direct proportion of transverse diameter to weight, thus showing that weight is the better index to transverse diameter.

In the early days of calorimetry the clinical value of accurate basal metabolism figures was greatly discounted by the lack of accurate means of estimation of the probable normal heat production for a given subject, and only when prediction tables for normal caloric output were made available did indirect calorimetry become a practical diagnostic procedure. The situation with regard to the use of the roentgen ray in cardiac disease has, in the past, been very similar as the roentgenologic technic in this field has developed rapidly, whereas prediction methods have scarcely kept pace. In 1918 Bardeen² published his now well known tables of normal measurements, but it was not until 1924 that P. C. Hodges and one of us (J. A. E. E.⁴) published a new set of prediction tables for cardiac area only, which were based on the statistical study of normal data and which, therefore, give optimal values for all variable factors. As would be expected, these tables show somewhat greater accuracy when analyzed mathematically, and present a method of prediction comparable to the well known prediction tables for basal metabolism.

The following data have been stripped of their mathematical under-structure, and are presented in more or less tabloid form because exactly

4 Hodges, P. C., and Eyster, J. A. E. Estimation of Cardiac Area in Man, *Am. J. Roentgenol.* **12**: 252-265 (Sept.) 1924. This article contains a useful bibliography of the subject.

TABLE 1—*Original Data*

Case	Age	Height	Weight	Cardiac Area	Transverse Diameter
1	34	170	53	91	97
2	18	180	68	113	102
3	28	175	61	91	105
4	28	173	61	102	105
5	28	168	54	98	107
6	31	170	75	103	107
7	46	168	72	82	107
8	28	185	60	93	108
9	23	173	57	93	108
10	30	175	72	101	109
11	33	178	67	105	110
12	25	180	68	107	110
13	45	178	64	112	111
14	28	178	62	102	112
15	32	173	64	108	112
16	26	175	66	106	113
17	27	185	78	126	113
18	33	183	73	102	113
19	29	178	62	115	113
20	32	173	67	110	113
21	30	178	64	107	114
22	27	178	68	113	114
23	25	183	63	106	114
24	28	175	68	105	114
25	27	173	70	113	115
26	23	175	64	125	115
27	20	179	62	115	115
28	30	170	67	92	115
29	28	168	55	99	115
30	32	170	70	104	115
31	23	163	56	92	115
32	34	175	76	112	116
33	18	176	62	110	117
34	32	168	64	117	117
35	31	180	68	115	117
36	19	173	66	118	119
37	33	178	74	117	120
38	24	159	55	103	120
39	26	173	64	110	120
40	26	170	60	119	121
41	46	170	74	105	121
42	30	163	61	103	121
43	33	165	60	106	122
44	30	168	67	104	122
45	22	175	66	124	123
46	47	182	82	124	124
47	30	180	70	118	125
48	27	175	72	113	125
49	43	183	84	122	125
50	28	164	62	106	126
51	34	173	64	119	126
52	29	180	84	96	126
53	24	185	68	117	126
54	37	192	77	143	127
55	33	179	66	112	127
56	37	192	77	143	127
57	30	178	70	123	128
58	28	175	74	115	129
59	59	170	57	117	129
60	26	175	73	119	130
61	28	178	75	117	130
62	30	173	77	108	131
63	33	168	68	100	131
64	34	173	64	135	132
65	27	174	85	105	132
66	25	173	68	118	134
67	45	171	79	113	134
68	50	183	77	143	135
69	26	183	77	128	136
70	33	179	70	139	136
71	27	178	73	113	136
72	29	178	73	120	137
73	28	172	61	124	137
74	29	178	75	129	139
75	35	173	75	112	139
76	52	178	79	126	140
77	35	175	79	128	140
78	31	180	83	121	142
79	34	185	98	123	142
80	34	179	86	132	147
Total	2,488	14,037.1	5,533.0	9,015	9,742
Mean	31.100	175.463	69.162	112.687	121.775
Sigma	7.4020	6.0785	8.3669		10.9109

the same formulas have been adapted to this work which were previously presented so completely by P C Hodges and one of us (J A E E). The various preliminary coefficients necessary for the formulation of the final equation will be found systematically listed in a footnote for the benefit of those desiring to follow the mathematics step by step. In the prediction tables which present the results of this work in a usable form, the previously published tables for area have been incorporated for the sake of convenience.

DATA

The original seventy cases from the measurements of which P C Hodges and one of us (J A E E) computed the prediction formula for cardiac area, augmented by ten additional normals, have been used as a basis for transverse diameter estimation. The selection of these cases was based, as before, in every instance on an exhaustive physical examination, including history, roentgen-ray studies and electrocardiograms, and no case with any suggestion of cardiac abnormality, whether accidental murmur, occasional ventricular extrasystole or simply sinus arrhythmia was included. All of the subjects are males, taken from the student body of the University of Wisconsin, the group of cases examined for the U S Veterans Bureau and from private practice.

In order to determine the correlation of the criterion, in this case transverse diameter, with all other variables when each has been given its optimal value, an interesting group of zero order coefficients must first be obtained. These correlations show the relationship between every possible pair of variables, and will be found listed in Table 2. Perfect correlation or parallelism between any two factors is indicated as unity (1.0). Obviously perfect correlation is not to be expected between any two variables in a study such as this, a correlation of 0.5 or better being considered good. It will be noted that of all the variables, weight has the greatest effect on (the best correlation with) transverse diameter, its actual figure being 0.5738. Age, which shows the next best correlation, is far less important than weight in determining transverse diameter, for its figure is only 0.2371. Height is of still less value with a correlation of 0.2140.

It is interesting to note at this point that in developing the formula for cardiac area P C Hodges and one of us (J A E E) found height to correlate best with the criterion, 0.5337, weight next, with 0.4533, and age last, with 0.1241. Probably the fact that height is the most important single factor in determining area is largely responsible for the low degree of inverse proportion between height and transverse diameter, because tall subjects having greater area show, therefore, wider diameter irrespective of heart position. Valuable as these simple correlations are in yielding concrete information as to the relative effect of body measure-

ments on the measurement we are studying, they can be used to far greater advantage by carrying the mathematics further and developing in succession correlations of increasing complexity until by substituting these values in a regression equation a formula is obtained by which one is enabled to estimate the most probable transverse diameter in any given individual by assigning to his age, height and weight measurements their optimal value in affecting transverse diameter. This formula is devel-

TABLE 2—Outline of Mathematical Treatment of Data

	Means	Squares of Means	Means of Squares	Sigmas
Age	31.1	967.21	1,022.000	7.4020
Height	175.463	30,787.2644	30,824.212	6.0785
Weight	69.162	4,783.3822	4,853.387	8.3669
Transverse diameter	121.775	14,829.1506	14,948.200	10.9109
Predicted transverse diameter	121.787	14,832.073	14,876.462	6.6625

$M_{T-D} \times A = 3,806.350$	$M_A \times W = 2,168.3750$
$M_{T-D} \times H = 21,381.075$	$M_H \times W = 12,161.7000$
$M_{T-D} \times W = 8,474.587$	$M_{T-D} \times P = 14,872.762$
$M_A \times H = 5,459.7875$	

Zero Order Correlation Coefficients	First Order Coefficients	
$r_{T-D A} = 0.2371$	$r_{T-D A W} = 0.0962$	$r_{A W H} = 0.2914$
$r_{T-D H} = 0.2140$	$r_{T-D H W} = -0.1189$	$r_{T-D W A} = 0.5433$
$r_{T-D W} = 0.5738$	$r_{A H W} = -0.0995$	$r_{A H T-D} = 0.0143$
$r_{A H} = 0.06421$	$r_{H W A} = 0.5329$	$r_{T-D H A} = 0.2088$
$r_{A W} = 0.2816$	$r_{T-D W H} = 0.5553$	$r_{A W T-D} = 0.1830$
$r_{H W} = 0.5177$	$r_{T-D A H} = 0.2292$	$r_{H W T-D} = 0.4947$

Second Order Correlation	Partial Standard Deviation
$r_{T-D A H W} = +0.0851$	$S_{D T-D A H W} = 10.3664$
$r_{T-D H A W} = -0.1106$	$S_{D A T-D H W} = 7.0437$
$r_{T-D W A H} = +0.5244$	$S_{D H T-D A W} = 5.1424$
$r_{A W T-D H} = +0.2027$	$S_{D W T-D A H} = 5.7805$
$r_{H W T-D A} = +0.5117$	

Validity of Prediction
$r_{T-D A H W} = 0.587707$ (direct order)
$r_{T-D A H W} = 0.586856$ (indirect order)
$r_{T-D P}$ (zero order correlation between measured and predicted T-D) = 0.579
Probable error of distribution = 7.36
Probable error of estimate = 4.82
Efficiency of prediction = $1 - \sqrt{1 - R^2} = 19\%$

oped by the Thuistone-Hull method and, based on the data taken from the original eighty cases, is written

Predicted $TD = +0.1094 \times A - 0.1941 \times H + 0.8179 \times W + 95.8625$, in which TD equals transverse diameter, A , age, H , height, and W , weight. This formula or equation can be translated into the following language. The probable normal cardiac transverse diameter of any male subject can be most accurately estimated by adding the products of

$0.1094 \times \text{age}$, $0.8179 \times \text{weight}$, subtracting from this sum the product of $0.1941 \times \text{height}$ and adding to the remainder the fixed figure 95 8625

For the sake of convenience the effect of age on transverse diameter has been computed for the various decades of life and since the effect of age is so slight as to make little difference in the final figure, the simple procedure of adding to the height-weight values 1 mm of transverse diameter for every decade can be employed without loss of accuracy. Again for the sake of convenience the factor for height ($—0.1941$) has been multiplied by the entire range of figures from 150 to 200 cm and the constant 95 8625 has been added to each of these and the final figures listed in tabloid form. Another portion of this table lists all weights between 50 and 100 Kg each multiplied by the weight factor (0.8179). This table makes possible the ready computation of transverse diameter predictions by simply adding to the transverse diameter value opposite the correct weight figure the transverse diameter value opposite the height figure, and adding one more millimeter for each decade of age.

The formula on which these tables are based permits of mathematical verification by the following method. The correlation of the criterion, TD , with the entire team of variables when each of these variables is given its optimal weight gives a figure that represents the degree of parallelism between the entire combination of variables and the criterion. This figure can be obtained by solving two similar equations, the only difference being the order in which values are introduced. If these two figures are identical or approximate each other closely one can be sure that no gross errors in arithmetic exist. The two figures so obtained are 0.587 and 0.588. If one applies the finished prediction formula to the original cases studied and then correlates the predicted transverse diameters against the measured transverse diameters, it will be seen that a correlation value should result which is identical with the figures just given. When this is done in this problem, correlation between TD and P (predicted transverse diameter), the resulting figure reads 0.579, showing a discrepancy easily explained by the dropping of decimals.

It can be readily understood that the more closely this final correlation figure approximates unity, the more efficient will be the prediction formula itself, for if we were able by any formula to predict the exact normal transverse diameter in every case the correlation between predicted values and measured values would be 1.0, or perfect correlation. It is perfectly true that 0.58 represents only fair prediction ability, and yet it can be shown that this method definitely decreases the probable error which would exist if one depended entirely on pure guesswork for estimating normal diameter. As a matter of fact, the efficiency of this formula is 19 per cent, which means that it is 19 per cent more efficient than assuming an average for all cases. Expressed in other

words, the probable error of distribution, where guesswork is employed, is 7.36, whereas the formula reduces this error to a probable error of estimate of 4.82

It is evident from the foregoing that this formula, as well as all other available means for predicting normal cardiac measurements,

TABLE 3—*Prediction for Normal Cardiac Area and Transverse Diameter*

$$\text{Predicted T-D} = +0.1094 \times A - 0.1941 \times H + 0.8179 \times W + 95.8625$$

I				II			
Stature		Area, Sq Cm	Transverse Diameter, Mm	Weight		Area, Sq Cm	Transverse Diameter, Mm
Cm	In			Kg	Pounds		
150	59	66.7	66.74	50	110	17.00	40.90
151		67.67	66.55	51	112.2	17.34	41.71
152	60	68.44	66.36	52	114.4	17.68	42.53
153		69.31	66.16	53	116.6	18.02	43.35
154		70.18	65.97	54	118.8	18.36	44.17
155	61	71.05	65.77	55	121	18.70	44.98
156		71.92	65.58	56	123.2	19.04	45.80
157		72.79	65.39	57	125.4	19.38	46.62
158	62	73.66	65.19	58	127.6	19.72	47.44
159		74.53	65.00	59	129.8	20.06	48.26
160	63	75.40	64.80	60	132	20.40	49.07
161		76.27	64.61	61	134.2	20.74	49.89
162		77.14	64.42	62	136.4	21.08	50.71
163	64	78.01	64.22	63	138.6	21.42	51.53
164		78.88	64.03	64	140.8	21.76	52.35
165	65	79.75	63.83	65	143	22.10	53.16
166		80.62	63.64	66	145.2	22.44	53.98
167		81.49	63.45	67	147.4	22.78	54.80
168	66	82.36	63.25	68	149.6	23.12	55.62
169		83.23	63.06	69	151.8	23.46	56.44
170	67	84.10	62.86	70	154	23.80	57.25
171		84.97	62.67	71	156.2	24.14	58.07
172		85.84	62.47	72	158.4	24.48	58.89
173	68	86.71	62.28	73	160.6	24.82	59.71
174		87.58	62.09	74	162.8	25.16	60.52
175	69	88.45	61.89	75	165	25.50	61.34
176		89.32	61.70	76	167.2	25.84	62.16
177		90.19	61.50	77	169.4	26.18	62.98
178	70	91.06	61.31	78	171.6	26.52	63.80
179		91.93	61.12	79	173.8	26.86	64.61
180	71	92.80	60.92	80	176	27.20	65.43
181		93.67	60.73	81	178.2	27.54	66.25
182		94.54	60.53	82	180.4	27.88	67.07
183	72	95.41	60.34	83	182.6	28.22	67.89
184		96.28	60.15	84	184.8	28.56	68.70
185	73	97.15	59.95	85	187	28.90	69.52
186		98.02	59.76	86	189.2	29.24	70.34
187		98.89	59.56	87	191.4	29.58	71.16
188	74	99.76	59.37	88	193.6	29.92	71.98
189		100.63	59.18	89	195.8	30.26	72.79
190		101.50	58.98	90	198	30.60	73.61
191	75	102.37	58.79	91	200.2	30.94	74.43
192		103.24	58.59	92	202.4	31.28	75.25
193	76	104.11	58.40	93	204.6	31.62	76.06
194		104.98	58.21	94	206.8	31.96	76.88
195		105.85	58.01	95	209	32.30	77.70
196	77	106.72	57.82	96	211.2	32.64	78.52
197		107.59	57.62	97	213.4	32.98	79.34
198	78	108.46	57.43	98	215.6	33.32	80.15
199		109.33	57.23	99	217.8	33.66	80.97
200	79	110.20	57.04	100	220	34.00	81.79

To find normal transverse diameter for a given individual, add T-D figure for stature to T-D figure for weight and to this total add 1 mm for every decade of age, e. g., height, 6 feet, weight, 187 pounds, age, 50 = 134.86 mm T-D or 60.34 + 69.52 + 5

leaves much to be desired in the way of efficiency, for 19 per cent is, at best, only a slight improvement over random guessing. There is, of course, a definite possibility of improving the efficiency of the formula, but the data in hand is insufficient to accomplish this. What one must

have in order to improve the formula is a new variable which correlates weakly with age, height and weight, and at the same time strongly with the transverse diameter. Variables that suggest themselves are girth, anteroposterior chest diameter and vital capacity. Undoubtedly, these will bear testing and it is possible that some one of these will be of value, though there is already information available to show that all of these measurements bear a fairly close relationship to height and weight, and if their intercorrelation figures are high as compared to their individual correlations with transverse diameter, their addition to the formula will be of slight value.

It remains to be seen by comparing the measurements of a group of known pathologic hearts with these tables just how great an individual deviation from predicted normal one must obtain to diagnose with certainty the existence of pathology in any one subject. However, by making use of Thorndike's tables based on a population of 10,000 people, the results of transverse cardiac diameter prediction in a large group can be demonstrated in advance. If we suppose that one were to find after predicting from age, height and weight in 10,000 persons that our formula (with its probable error of 4.82 mm) had assigned to each a transverse cardiac diameter value of 100 mm, the actual measurement of these same subjects by othodiagraphic means would show 5,000 hearts between 95 and 105 mm, 2,500 hearts larger than 105, and 2,500 hearts smaller than 95. Three-fourths of these cases, therefore, would not exceed 100 mm by more than 5 mm, or conversely the odds would be three to one against a normal subject having a measured cardiac transverse diameter that would exceed his predicted diameter by more than 5 mm.

SUMMARY

1 New tables are presented for the estimation of normal transverse cardiac diameter in man. These tables are based on the following prediction formula: Transverse diameter in millimeters equals $\text{age } 0.1094 - \text{stature } 0.1941 + \text{weight } 0.8179 + \text{the constant } 95.8625$.

2 The tables given here introduce a means of prediction that is 19 per cent efficient.

3 New variables that have but slight relation to age, height and weight while paralleling transverse diameter rather closely must be sought in order to improve this formula.

4 If the heart is found to be 5 mm wider in its greatest transverse diameter than the diameter as predicted by this formula, the chances are three to one that the widening is pathologic.

THE EFFECT OF LEAD AND RADIUM ON MATURE AND IMMATURE RED BLOOD CORPUSCLES

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The epoch making discoveries of the Roentgen rays by Roentgen and of radium by the Curies have lead rapidly to much knowledge of vital processes and to the alleviation of disease. One of the most useful clinical applications of these radiations is in the therapy of cancer. The application of radio-active substances does not always result in destruction of the tumor, but their beneficial effects are such as to warrant the search for a means of increasing their destructive properties. It has been suggested that this may be accomplished by introducing into the tissue some substance to augment the production of secondary radiation. Lead, among other substances, has been tried in the belief that it enters cancer tissue and young cells more readily than normal tissue or adult cells.

For determining the effect of irradiation on tissues, with and without the presence of substances causing secondary radiations, animal cancer transplants are unsatisfactory. The great variations in the rate and duration of growth and reaction to treatment of these neoplasms is well known and makes the interpretation of the effect of therapy both difficult and uncertain. It was decided, therefore, to determine if information could be obtained from a study of blood cells to warrant further consideration of the problem. Erythrocytes furnish suitable test cells for this purpose. This is because not only may they be obtained in varying degrees of maturity but also their hemolysis furnishes a quantitative index of cell destruction. It is recognized that the behavior of immature, as contrasted with adult red blood corpuscles, does not necessarily indicate that a similar action occurs with cancer and normal tissue cells.

METHOD

The effect of lead, radium emanation and combinations of the two was tested on mature and immature red blood cells in various ways. Each of the experiments recorded was repeated not less than five times to insure the correctness of the observations.

Normal rabbits were rendered anemic by repeated withdrawal of blood from the heart. Previous to and during the period of bleeding

* From the medical service of the Collis P Huntington Memorial Hospital of Harvard University. This paper is No. 59 of a series of studies on metabolism from the Medical School of Harvard University and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Medical School of Harvard University for the study of chronic diseases.

observations were made on the red blood cell count, the percentage of hemoglobin and reticulocytes, and the "fragility" of the red cells in hypotonic sodium chlorid solutions. It was hoped to obtain a comparison of effects of the substances on the reticulated and the adult red corpuscles from the blood of the same animal. This was attempted repeatedly but was found to be impracticable. Therefore, when the blood contained from 30 to 50 per cent reticulated erythrocytes it was used for a comparison with that of a normal rabbit whose blood consisted almost entirely of adult cells. The term "immature cells" is used in the text to denote erythrocytes obtained from a rabbit whose blood contained more than 30 per cent reticulocytes. The term "adult cells" is used to indicate red blood corpuscles obtained from an animal having less than 35 per cent reticulated erythrocytes in the peripheral circulation.

Approximately 30 cc of blood were withdrawn from a normal rabbit and shortly afterward from an anemic rabbit. The tests referred to above were made on each specimen. These bloods were gently defibrinated, washed serum free with modified Ringer's solution,¹ and suspended in it in a concentration of approximately 40 per cent. Each of these two suspensions of corpuscles then was divided into four equal portions. The first was allowed to stand in the Ringer's solution for the duration of the experiment and served as a control. The second was exposed to an equal volume of 0.001 per cent lead chlorid solution for one hour, which, as has been shown by Aub, Reznikoff and Smith,² is sufficient to "lead" red cells. These cells were then washed free of the lead solution and resuspended in Ringer's solution for the remainder of the experiment. The third fraction was similarly treated with lead and after being washed was exposed to radium emanation. The fourth portion was irradiated only.

The red cells in each of the eight samples, after being washed, were subjected to various strengths of hypotonic salt solution to test their resistance to hemolysis. This test was conducted as follows. One cubic centimeter portions of sodium chlorid solutions, ranging in strength from 0.9 to 0.04 per cent with a variation of 0.02 per cent between each solution, were placed in test tubes. To each was added 0.15 cc of a 20 per cent suspension of cells. After these preparations had stood in the cold for ten hours the percentage of hemolysis was determined by direct comparison with standards.

Suspensions of each of the eight different samples also were allowed to stand for ten hours in the cold. The percentage hemolysis then

1 The Ringer's solution was carbonate and phosphate free and contained sodium chlorid, 0.9 per cent, potassium chlorid, 0.042 per cent, and calcium chlorid, 0.024 per cent.

2 Aub, J. C., Reznikoff, P., and Smith, D. E. Lead Studies, III, The Effects of Lead on Red Blood Cells, *J. Exper. Med.* 40: 151 (Aug.) 1924.

resulting was determined by comparison with standards in a Duboscq colorimeter

All solutions were maintained as near as possible at p_H 6.5

The radio-active substance used was radium emanation collected and purified by the method of Duane³ and contained in evacuated tubes of 1 by 6 cm size, which were drawn out to a capillary tip at either end. These tubes were allowed to stand overnight before the cells were exposed to allow the emanation to reach an equilibrium with its decomposition products. The quantity of the emanation was then measured by means of the method and apparatus described by Duane³. One of these tubes was immersed beneath the surface of the cells suspension, its capillary tip was broken off, and the suspension was carried into the tube by negative pressure. The broken tip was immediately sealed with paraffin. From time to time the tube was gently agitated to insure a uniform mixture of the contents. This is, in all essentials, the method described and used by Redfield and Bright,⁴ and since the emanation is in solution it affords a convenient method of irradiating fluids. As the alpha, beta and gamma rays all act on cells in suspension, doses of only one millicurie hour are required. Whenever results were to be compared the same amount of emanation was used.

THE "FRAGILITY" OF ERYTHROCYTES TO HYPOTONIC SODIUM CHLORID SOLUTIONS

1 *Controls*—It was noted that the erythrocytes from rabbits rendered anemic by chronic blood loss were invariably more resistant to hypotonic salt solution than the cells of the same rabbit prior to bleeding. This is in accord with and confirmatory of the results obtained by Minot and Weld⁵. Apparently it is one of nature's provisions for the preservation of a competent circulating blood after prolonged hemorrhage.

Likewise, it was noted that there is a difference in the resistance of the erythrocytes to hypotonic salt solutions immediately and some time after their withdrawal from the circulation. Cells that have stood several hours are less easily hemolyzed than those which have been obtained recently from the circulating blood. This phenomenon was observed constantly and is in accord with the work of Ashby⁶ and others. Thus,

3 Duane, W. Methods of Preparing and Using Radio-Active Substances in the Treatment of Malignant Disease, and of Estimating Suitable Dosages, Boston M. & S. J. **177** 787 (Dec. 6) 1917.

4 Redfield, A. C., and Bright, E. M. Hemolytic Action of Radium Emanation, *Am. J. Physiol.* **65** 312 (July) 1923, The Physiological Action of Ionizing Radiations, *ibid.* **68** 354 (April) 1924.

5 Minot, G. R., and Weld, M. Unpublished observations.

6 Ashby, W. A Study of the Mechanism of Change in Resistance of Erythrocytes to Hypotonic Salt Solutions, *Am. J. Physiol.* **68** 250 (April) 1924.

the only proper controls for the experiments described are tests on red cells from the same animals that have stood for the same amount of time as those subjected to the various procedures

2 *Effect of Lead*—Aub, Reznikoff and Smith² have shown that when erythrocytes are exposed to 0.01 mg of lead as chlorid per cubic centimeter of cell suspension, their resistance to hypotonic salt solutions is greatly increased. The degree of this action of lead depends on the concentration, the time of exposure and the temperature. These investigators did not determine a difference in the effect of lead on immature and mature red corpuscles. In the experiments here reported it was repeatedly noted that lead affected the resistance of

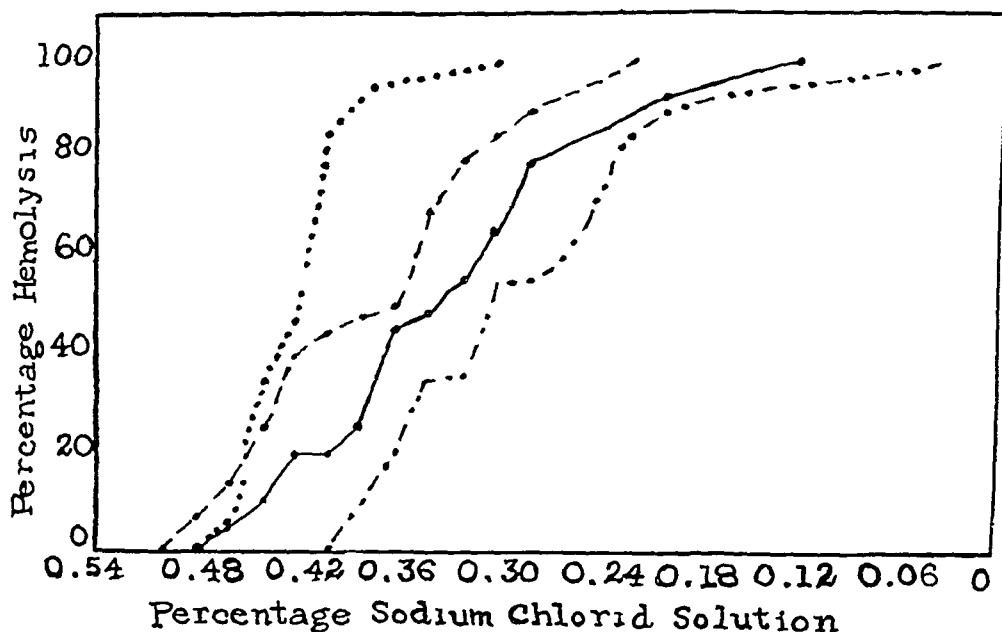


Fig 1—Effect of lead on “fragility” of mature and immature erythrocytes. dotted line, control adult cells, dots and dashes, treated adult cells, broken line, control immature cells, solid line, treated immature cells

erythrocytes from a normal rabbit much more than it did those from an anemic animal having a large number of immature red cells. This finding was constantly observed and is illustrated in Figure 1. The figure shows that the difference between the point of complete hemolysis of the mature “leaded” cells and their control and between the immature “leaded” cells and their control is in the ratio 2.5 : 1. Although the differences between the points of initial hemolysis are not so great, yet the “resistance span” (the range between initial and complete hemolysis) of the adult “leaded” cells is greater than that of the young “leaded” cells. The degree of difference apparently fluctuated with the relative number of immature cells present, but the greater effect of lead on adult cells than on young cells was a constant finding.

3 *Effect of Radium*—Irradiation from radium emanation did not affect the resistance of either immature or adult cells to hypotonic salt solutions. As is shown in Figure 2 the curves for the percentage of hemolysis of the control and irradiated cells do not vary beyond the range of experimental error.

4 *Effect of Lead and Radium*—The experiments showed that when adult or immature cells are exposed to lead and then to radium the effect produced on their fragility to saline solutions is midway between the effect of either alone. Figures 1, 2 and 3 show that lead tends to lengthen the "resistance span," radium tends to make it similar to the control, but when both lead and radium are used the curve is a combination of these two effects.

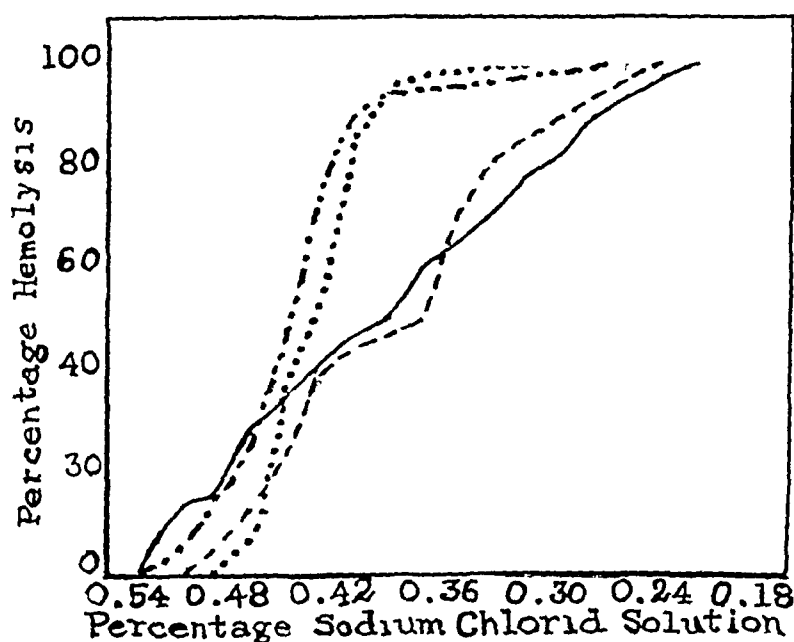


Fig 2—Effect of radium on "fragility" of mature and immature erythrocytes: dotted line, control adult cells, dots and dashes, treated adult cells, broken line, control immature cells, solid line, treated immature cells.

Thus, erythrocytes have an increased resistance to hemolysis by hypotonic salt solutions following chronic blood loss, on standing several hours in Ringer's solution, and after exposure to lead, while their resistance is unchanged by radium emanation. However, the foregoing experiments do not furnish information concerning the destructive action of radio-active substances on cells containing a heavy metal. For this purpose, one must turn to the direct hemolytic action of the substances employed.

THE HEMOLYTIC ACTION OF LEAD AND RADIUM

Numerous experiments were conducted to determine the hemolytic effect of lead, radium, and lead and radium combined on both immature and adult red cells.

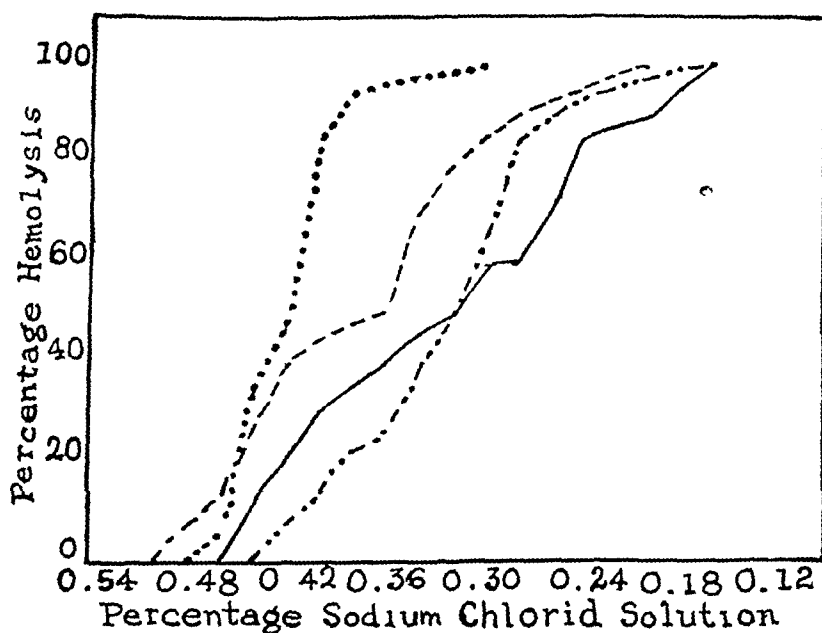


Fig 3—Effect of lead and radium on “fragility” of mature and immature erythrocytes dotted line, control adult cells, dots and dashes, treated adult cells, broken line, control immature cells, solid line, treated immature cells

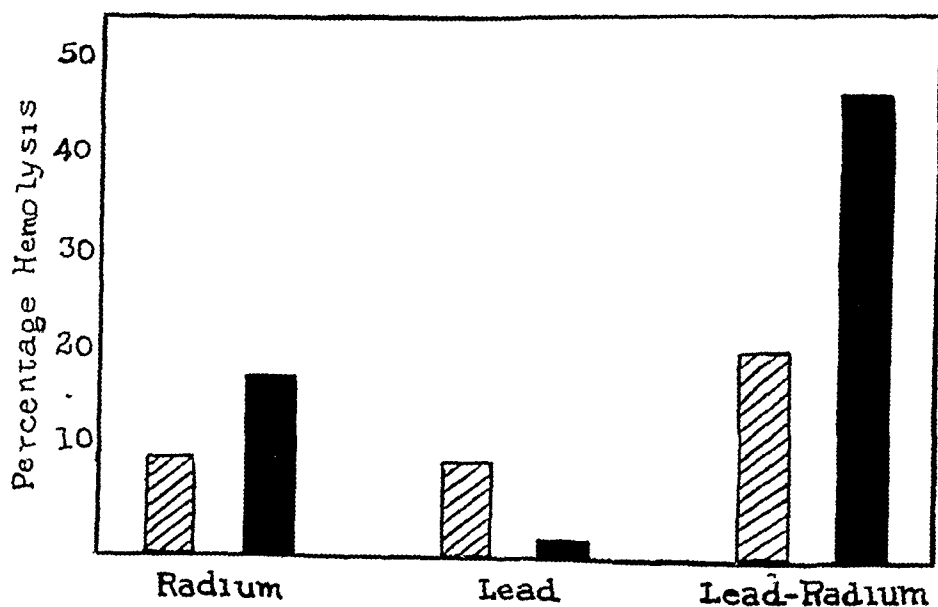


Fig 4—Hemolytic effect of lead, radium, and lead and radium on mature and immature erythrocytes broken lines, adult cells, solid lines, immature cells

Red blood corpuscles, when gently defibrinated, carefully washed, and centrifugated are not hemolyzed. Their exposure to a sufficient amount of lead causes them to become very brittle, as Aub, Reznikoff and Smith² have shown. In the experiments recorded below manipulation of these "leaded" cells was done with the greatest care to prevent hemolysis by trauma. Old and young cells were subjected to the action of lead, radium, and lead and radium by the methods described above.

The results obtained in five typical experiments conducted to determine the hemolytic effect of lead and radium on old and young cells are summarized and shown graphically in Figure 4. It will be observed that the adult cells are more easily hemolyzed by lead than are the immature cells, while radium affects the cells in just the opposite manner. The irradiation of cells previously exposed to lead causes a marked increase in the amount of hemolysis. This destructive action is twice as marked on young cells as on adult cells.

The Hemolytic Effect of Various Exposures of "Leaded" Immature and Mature Erythrocytes to Radium Emanation

Time of Exposure to One Millicurie of Radium Emanation	Percentage of Hemolysis of Immature Cells*	Percentage of Hemolysis of Adult Cells†
½ hour	5	2
1 hour	53	25
1½ hours	80	35

* Erythrocytes from a rabbit having 2,100,000 per cubic millimeter, hemoglobin, 35 per cent, Sahli, reticulocytes, 46 per cent.

† Erythrocytes from a rabbit having 5,600,000 per cubic millimeter, hemoglobin, 101 per cent, Sahli, reticulocytes, 15 per cent.

The effect of radium was so greatly enhanced by the secondary radiation obtained from the presence of lead that determinations were made of the influence of various lengths of exposure of "leaded" cells to the radio-active substance. Because of the difficulty of accurately measuring the small amount of emanation used a constant amount of radium was employed and the time of exposure varied. The results of a typical experiment are given in the accompanying table. The data illustrate that the hemolytic action of radium rays in the presence of a heavy metal varies with the length of exposure. Even so, the effect on young red cells bears a constant relationship to that on mature erythrocytes, while the degree of hemolysis depends on the amount of irradiation.

COMMENT

The observations on the "fragility" of old and young red blood corpuscles in hypotonic sodium chlorid solutions after exposure to lead, radium and combinations of the two, are set forth without further comment. They serve to indicate distinctions between old and young red cells. These "fragility" tests when compared with those on the hemolytic effects of lead and radium also illustrate that one form of

injury to a cell does not necessarily indicate that a similar effect will occur from other deleterious agents

Henri and Mayer,⁷ Chambers and Russ,⁸ Solmanson and Dreyer,⁹ Hansman,¹⁰ and Redfield and Bright⁴ have shown that radium rays have the ability to hemolyze red blood corpuscles. The alpha particles are chiefly responsible for this action.¹¹ In the experiments here reported alpha, beta and gamma rays of the emanation have been in solution in the red cell suspensions. This permits only one one-hundredth as much emanation to produce the same results as when beta and gamma rays alone are used.⁴

It is well known that when radio-active rays are absorbed by matter secondary radiations are liberated. If the radiator be a metal the intensity of this emission increases with the atomic weight of the metal, but the penetrating power of the rays is unaltered.¹² Redfield and Bright⁴ have shown that the penetration of the secondary corpuscular radiation into protoplasm is in the range of 0.003 cm. Hence, in the case of erythrocytes the effect is largely on the cell membrane. From the work of Aub, Reznikoff and Smith² it is evident also that lead acts on the surface of erythrocytes. These facts explain clearly why the experiments demonstrate that the hemolytic action of radium emanation on erythrocytes is greatly increased by the presence of a heavy metal. The "leaded" red blood corpuscles were bombarded by the rays of the emanation and it is very probable had generated in their cell membranes an intense amount of secondary radiation with consequent damage to the membranes and hemolysis.

The question arises why lead hemolyzes the mature more than it does the immature red cells. This may be because young erythrocytes are of a firmer composition than old ones, as is suggested by the greater resistance of immature cells to heat.¹³ Furthermore, as Buckman and MacNaugher¹⁴ have shown, normal young red cells appear to with-

7 Henri, V, and Mayer, A. Action des radiations du radium sur les colloïdes, l'hémoglobine, les ferments et les globules rouges, *Compt rend Acad. d sc* **138** 521, 1904

8 Chambers, H, and Russ, S. The Action of Radium Radiations Upon Some of the Main Constituents of Normal Blood, *Proc Roy Soc* **84** 124, 1911-1912

9 Solmanson C J, and Dreyer, G. De la loi de l'effet hemolytique des rayons d Becquerel, *Compt rend Acad d sc* **144** 999, 1907

10 Hansman, W. Ueber Hamolyse durch Radium strahlen, *Wien klin Wchnschr* **29** 1289, 1916

11 Chambers and Russ (Footnote 8) Redfield and Bright (Footnote 4)

12 Sadler, C A. Homogeneous Corpuscular Radiation, *Philosophical Mag* **19** 337, 1910

13 Isaacs, R, Brock, B, and Minot, G R. The Resistance of Immature Erythrocytes to Heat, *J Clin Invest* **1** 425 (June) 1925

14 Buckman, T E, and MacNaugher, E. The Relative Fragility of Reticulated Red Corpuscles, *I M Research* **44** 61 (Sept) 1923

stand hemolysis by hypotonic salt solution better than do adult cells. This property of immature erythrocytes may be analogous to their greater resistance to the injurious effect of lead. Another factor of influence is perhaps the difference in the chemical composition of cells of different ages. It is believed by many that young cells of various types have a higher phosphorus content than old cells. Buckman, Minot, Daland and Weld¹⁵ have pointed out that this appears to be true for immature red blood corpuscles. The action of lead on red cells has been explained clearly by Aub, Reznikoff and Smith² to be due to its union with the inorganic phosphates of the cell. These authors likewise have shown that the diffusion of the inorganic phosphates from the red blood corpuscles into the surrounding medium prevents the action of lead on the cell. It will be recalled that in the tests recorded above the erythrocytes were suspended in Ringer's solution before adding an equal volume of 0.001 per cent lead chloride solution. It is possible that by virtue of a higher phosphate content of the immature cells more phosphates diffused into the Ringer's solution and thus prevented the effect of the lead on these cells.

The destructive action of radio-active rays is always more marked on immature than on mature cells. Thus, it was to be expected that radium emanation would cause greater hemolysis of young than of old red blood cells. The experiments also demonstrate that a given amount of lead and radium combined hemolyze about twice as many immature corpuscles as mature ones. It is plausible to believe that these result from the damage produced by the secondary radiation emanating from the insoluble lead phosphate present on the cell membrane. Even though, as suggested above, less lead may be present on young than on old cells, it may well be that, like human tumors, an increase in irradiation injures immature much more than mature cells.

It is not intended to convey the impression that the experiments here presented have a direct bearing on the therapy of malignant disease. The fact that a heavy metal increases the destructive effect of radio-active substances and that this action is more pronounced on immature than mature red cells might be applied to the treatment of cancer. However, to do so it is necessary to find a metal of sufficiently high atomic weight which concentrates in the tumor in amounts adequate to give effective therapeutic results. The report by Bell¹⁶ concerning the treatment of 122 patients with cancer by intravenous injections of different lead compounds is interesting in this connection. This author reports favorable results, but does not appear to have presented evi-

15 Buckman, T. E., Minot, G. M., Daland, G. A., and Weld, M. Blood Phosphorus. Its Relation to Cancer and Anemia, *Arch. Int. Med.* **34**:181 (Aug.) 1924.

16 Bell, W. B. The Influence of Lead on Normal and Abnormal Cell Growth, *Lancet* **1** 267 (Feb. 9) 1924.

dence that lead actually enters the tumor. Some results obtained by Minot¹⁷ tend to show that after intravenous injection of lead compounds into mice with tumors only minute amounts of lead may be found in the cancer, while the major part of that injected is present in other parts of the body.

SUMMARY

1 Control tests confirm the work of others that erythrocytes following chronic blood loss, on standing several hours in Ringer's solution, and after exposure to lead as chlorid have an increased resistance to hemolysis by hypotonic saline solutions.

2 The "fragility" to hypotonic saline solutions of young and old erythrocytes previously subjected to lead, radium emanation and combinations of the two is as follows:

(a) Lead produces a greater increased resistance of mature than immature red blood corpuscles.

(b) Irradiation with radium emanation does not change the resistance of mature or immature erythrocytes.

(c) Lead and radium combined produce an effect midway between the effect of either alone.

3 The hemolytic action of lead, radium emanation and lead and radium combined on young and old erythrocytes is as follows:

(a) Radium hemolyzes more readily immature than mature red blood corpuscles.

(b) Lead has just the opposite effect from radium.

(c) Irradiation of "leaded" erythrocytes greatly increases the amount of hemolysis above that produced by either agent alone. This effect is twice as great on "leaded" immature as on "leaded" mature red blood corpuscles.

¹⁷ Minot, A. S. Personal communication to the author.

BLOOD CHANGES IN THE ANTEPARTUM AND THE POSTPARTUM PERIOD OF YOUNG MOTHERS

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AND

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Some work in Harlem Hospital in which we were attempting to ascertain the factor that predisposes children to rickets by a systematic survey of the phosphorus of the blood of mothers and infants suggested a study of wider scope, including not only the inorganic phosphorus but also other constituents of the blood during the critical period of child formation in the uterus

Early investigators have had continual controversies regarding the significant chemical changes that occur in the inorganic constituents of normal pregnant women. The recent work of Denis and King¹ in which from 9 to 11 mg per hundred cubic centimeters of blood is accepted as representing the standard for normal serum calcium is corroborative of these earlier studies in which no change was predicated. Of all the workers in the field, however, Widdows² is the only one who reaches her conclusion by analyses of the blood of the same woman at definite periods of pregnancy. She finds that in most, but not in all, cases there is a tendency to a decrease in the calcium content of the blood in late pregnancy and a general tendency to rise directly after confinement, and Denis and King admit that "whether it would have been possible to demonstrate a progressive lowering of the serum calcium in individual cases, had they been able to obtain specimens of blood from the same subjects at different times during pregnancy, could only be shown by further work on this subject."

We have undertaken this further work and included in our study not only the calcium factor but also phosphorus and creatinine of the blood, as well as creatinine of the urine. Furthermore, the work was extended to include the antepartum and the postpartum periods.

Our samples of blood were taken by means of a venous puncture in the afternoon, about four hours after dinner, and immediately

*From the chemical research laboratory of Fordham University and the chemical laboratory of Harlem Hospital

1 Denis, W, and King, E L. Am J Obst & Gynec 7 253 (March) 1924, *ibid* 7 409 (April) 1924

2 Widdows, S T. Biochem J 17 34, 1923

analyzed Lithium citrate was used as the anticoagulant. The twenty-four hour specimen urines were collected in the usual way. All the phosphorus and creatinine determinations were made on whole blood, the calcium analyses, on blood serum.

The value of any work may be estimated according to the methods used. For this reason we have adopted the following procedures. The calcium was determined by the technic of Kramer and Howland³. Three cubic centimeters of citrated whole blood was placed in a 15 cc centrifuge tube and centrifugated for five minutes. One cubic centimeter of the blood plasma was pipetted with an Ostwald pipet into a dry 15 cc centrifuge tube. To this was added 1 cc of a saturated solution of ammonium oxalate, after which the tube was rotated to mix the contents thoroughly and then set aside for one-half hour to allow precipitation. Once more the tube was centrifugated for five minutes and the supernatant fluid decanted. The precipitate was washed with 2 per cent ammonium hydroxide, centrifugated and again decanted. This procedure was repeated three times. Five cubic centimeters of 5 per cent sulphuric acid was then added, and the tube placed in a boiling water bath for five minutes. The liberated oxalic acid was then titrated with hundredth normal potassium permanganate, and the calcium determined by a factor.

The inorganic phosphorus was determined by the original method of Bell and Doisy⁴. This consists in precipitating the proteins with trichloroacetic acid, centrifugating, decanting the filtrate and precipitating the phosphorus with a solution of strychnine molybdate. After these operations had been performed the tube was centrifugated and the supernatant liquid decanted. This procedure was repeated three times. Finally the washed precipitate was dissolved in 6 cc of tenth normal sodium hydroxide, and the solution poured into a 200 cc volumetric flask. The test tube also was rinsed with distilled water into the same flask. Twenty cubic centimeters of 20 per cent potassium ferrocyanide was then added and also 10 cc of concentrated hydrochloric acid. The contents of the flask was then diluted to the mark with distilled water, thoroughly mixed, and matched against a standard solution whose phosphorus had gone through a similar procedure.

The Folin-Wu⁵ method was employed for the estimation of creatinine of the blood. Twenty-five cubic centimeters of a saturated solution of purified picric acid was transferred to a small clean flask and 5 cc of 10 per cent sodium hydroxide added. Ten cubic centimeters of blood filtrate was transferred into a small flask at the same time. Five

3 Kramer, B, and Howland, J. *J Biol Chem* **43** 35 (Aug) 1920

4 Bell, R. D., and Doisy, E. A. *J Biol Chem* **44** 55 (Oct) 1920

5 Folin, O., and Wu, H. *J Biol Chem* **38** 81 (May) 1919

cubic centimeters of standard creatinine was diluted to 20 cc in another flask, then 5 cc of freshly prepared alkaline picrate solution was added to the blood filtrate, and 10 cc to the diluted creatinine solution. After ten minutes the two solutions were compared in the colorimeter.

The original Folin⁶ method was used for the estimation of creatinine in the urine. One tube of the colorimeter was almost filled with 0.5 normal potassium bichromate and set to read 8 mm. Two cubic centi-

TABLE 1—Calcium in Blood (Milligrams per Hundred Cubic Centimeters)

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks						
				6	7	8	9	1	2	3	4	5	6	7
1	18	121 (54.9 Kg)	New York	12.08 11.44 11.93	11.89 11.10 12.12 11.86	11.98 11.41 11.37	10.10 12.00 11.06 11.42	11.31 10.96 11.71 9.60		10.49 10.53	11.60 11.32 11.41	11.22 12.20 11.91 11.33	10.93 10.74 11.00 10.99	11.37 11.80
2	14	119 (54 Kg)	New York				10.20 10.70 9.10							
3	15	100 (45.4 Kg)	Long Island				11.60							
4	17	135 (61.2 Kg)	New York				9.53 11.20	11.47 9.83 9.99 11.29	10.72 10.88					
5	14	120 (54.4 Kg)	Virginia				10.35 11.29 11.43	10.32 11.55 10.93 11.06						
6	16	152 (68.9 Kg)	South Carolina			10.66	11.73 13.49 11.65 10.88	12.40 11.87 11.21 11.61	10.37 11.36 11.42					
7	18	180 (81.6 Kg)	Virginia		11.21 10.36 10.53 10.57	12.00 11.93 11.06 11.39	12.14 12.20 11.90 12.31							
8	19	120 (54.4 Kg)	New York				10.76 11.64 11.55	11.98 10.42 11.33						
9	18	170 (77.1 Kg)	North Carolina				10.34 11.56	11.91 11.46	10.89 10.57 11.36					
10	13	128 (57.1 Kg)	South Carolina				12.27 12.39 11.77							
							12.11							

meters of urine was pipetted into a 100 cc volumetric flask, to which was then added 3 cc of saturated picric acid solution and 1 cc of 10 per cent sodium hydroxide. After five minutes the contents of the flask were diluted to the mark, thoroughly mixed and compared with the standard.

In our study we have confined ourselves to young negro girls, some of whom were born and bred in the South while others had been in

New York their entire lives. These girls were kept in a home in which they were all subjected to the same dietetic and hygienic conditions, eating the same food, and spending a similar number of hours in the open air. All of them showed negative Wassermann reactions and were primiparas. The blood and urine analyses, with only a few exceptions, were made every week. Unfortunately, our earliest admittance dates from the sixth month of gestation.

TABLE 2—*Inorganic Phosphorus in Blood (Milligrams per Hundred Cubic Centimeters)*

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks						
				6	7	8	9	1	2	3	4	5	6	7
1	18	121 (54.9 Kg.)	New York	2.41	2.19	2.54	2.22	1.98						
				2.39	2.30	2.01	2.31	2.31	2.17	2.03	1.76	1.65	2.32	2.31
				2.09	2.00	2.16	2.18	2.16		2.11	1.89	1.88	2.14	2.47
				2.13	2.09		2.05	2.33			2.36	1.92	2.20	2.23
2	14	119 (54 Kg.)	New York				2.92							
							2.76							
							2.59							
						2.90								
3	15	100 (45.4 Kg.)	Long Island				2.70							
							2.60							
4	17	135 (61.2 Kg.)	New York					3.61	3.21					
								3.00	2.99	2.87				
								3.12	2.74					
								3.10						
5	18	120 (54.4 Kg.)	Virginia				2.60	3.22						
							2.33	3.00						
							2.65	3.10						
						2.40	2.76							
6	16	152 (68.9 Kg.)	South Carolina			2.56	2.77	2.96						
						2.70	2.32	2.54						
						2.98	2.47	2.41						
					2.54	2.74	2.61							
7	18	180 (81.6 Kg.)	Virginia			2.90	2.64	2.53						
						1.86	2.33	2.70						
				3.10	2.47	2.70	2.44							
				2.51	2.82	2.71								
8	19	120 (54.4 Kg.)	New York				3.25	2.50						
							2.92	2.99						
							2.37	2.76						
9	18	170 (77.1 Kg.)	North Carolina							2.82				
										2.51				
										2.77				
10	13	128 (57.1 Kg.)	South Carolina											

The calcium determinations are given in table 1. In our studies these analyses were not made in random cases, as was true of the work of Denis and King, but on women throughout their entire gestation period, and in this respect the study resembles that of Widdows. The findings, however, are more in harmony with the work of Denis inasmuch as there was no significant change up to parturition. In these young women the calcium concentration was found to be 11.3 mg per hundred cubic centimeters, which is a trifle more than the 10.9 mg

found by Denis in her cases. It is to be noted, however, that the patients presented by Denis were mostly mature women and with a varying number of pregnancies. In only one of our cases was there an increase in the calcium content from the sixth to the ninth month ranging from 10.5 to 12.1 mg per hundred cubic centimeters, which in this instance was diametrically opposed to the findings of Widdows. With parturition there was a slight drop in the calcium, which lasted for three weeks and then returned to normal for this particular group. This

TABLE 3—Creatinine in Blood (Milligrams per Hundred Cubic Centimeters)

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks					
				6	7	8	9	1	2	3	4	5	6
1	18	121 (54.9 Kg)	New York	1.72	1.96	2.14	2.20	1.85		1.52	2.22	2.10	2.27
				1.79	2.12	2.33	2.16	2.13		1.37	2.01	2.17	2.31
				2.23	2.18	1.98	2.41	2.00		1.40	1.88	2.14	
2	14	119 (54 Kg)	New York	2.15	2.30		2.18	1.61			1.98	1.92	
							2.40						
							2.63						
3	15	100 (45.4 Kg)	Long Island			2.37	2.15						
4	17	135 (61.2 Kg)	New York					2.33	2.13				
								2.19	2.18	1.79			
								2.50	2.44				
5	18	120 (54.4 Kg)	Virginia					2.46					
6	16	152 (68.9 Kg)	South Carolina					1.54	1.22				
								1.30	1.56				
								1.60	2.01				
7	18	180 (81.6 Kg)	Virginia			1.83		1.75					
8	19	120 (54.4 Kg)	New York					2.03	2.22	1.98			
								2.36	2.20	2.12			
								2.41	1.87	2.16			
9	18	170 (77.1 Kg)	North Carolina					1.66	2.13	2.04			
10	13	128 (57.1 Kg)	South Carolina					1.63	1.75	2.30			
								1.72	2.09	2.17			
								2.14	1.98	2.06	1.88		
10	13	128 (57.1 Kg)	South Carolina					2.18	1.50	1.76	2.15		
10	13	128 (57.1 Kg)	South Carolina					2.10	2.40				
								2.15	2.60				
								2.27	2.33				
10	13	128 (57.1 Kg)	South Carolina							1.84			
										2.00			
										2.01			
10	13	128 (57.1 Kg)	South Carolina					1.73	2.33				
10	13	128 (57.1 Kg)	South Carolina							2.63			
										2.19			
										2.33			
10	13	128 (57.1 Kg)	South Carolina					2.17					

is obviously interrelated with the carbon dioxide capacity of the blood, since carbon dioxide determinations made during the postpartum period showed that immediately after delivery the carbon dioxide combining power of the blood dropped to about 30 with a gradual rise to normality up to the time of dismissal.

A detailed study of the table of the calcium in the blood brings out the interesting fact that the northern girls have a lower calcium concentration than the southern girls, the figures being 10.6 and 11.5 mg,

respectively. The cases reported by Denis which are in all respects comparable with those reported here, with the exception of gestation months, come to an average of 108 mg, which is identical with the average of our northern girls.

Hess,⁷ and later Denis, have reported inorganic phosphorus as being normal during pregnancy. This is confirmed by our data (table 2). In the postpartum period, however, we have found a slight drop, which

TABLE 4—Creatinine in Urine (Milligrams per Twenty-Four Hour Output)

Case	Age	Weight	Residence	Antepartum by Months				Postpartum by Weeks					
				6	7	8	9	1	2	3	4	5	6
1	18	121 (54.9 Kg)	New York	677 493 702	570 826	712 736	412 592 644 487	182 275 429		250 264 483	492	310 200 438	307
2	14	119 (54 Kg)	New York		641		609 533 601						
3	15	100 (45.4 Kg)	Long Island				398 650 711						
4	17	135 (61.2 Kg)	New York				572 759 793	200 292 313	124 186				
5	14	120 (54.4 Kg)	Virginia				491 587	174 332 301					
6	16	152 (68.9 Kg)	South Carolina			636	497	150 231 262					
7	18	180 (81.6 Kg)	Virginia	637 561 772	685 574 713	462	495 629						
8	19	120 (54.4 Kg)	New York				590 676 459	140 390 271					
9	18	170 (77.1 Kg)	North Carolina				613 723 519	306 359	220 146				
10	13	128 (57.1 Kg)	South Carolina				814 733 628	141 198 285					

may be significant, occurring in the third, fourth and fifth week after parturition. This slight drop, if it is significant, may be associated with the regeneration of impaired tissue. In the individual cases there was no significant difference between the average of the northern girl and that of the southern girl.

The creatinine content of the blood (table 3) of pregnant women has been determined in scattered cases by Denis and her co-workers and

7 Hess, A. F., and Matzner, M. J. Am J Dis Child 26:285 (Sept.) 1923

also by Killian and one of us⁸ Both of these found creatinine within normal limits, the former worker giving figures of a low norm whereas the latter gives figures within the high range of normal concentration In our data most of the analyses were within the high range and the averages of the various months of gestation show no significant change The postpartum period also shows no changes

Creatinine was also determined in the urine The analyses are given in table 4, and are tabulated in milligrams for the twenty-four hour output During the development of the fetus the creatinine of the blood was found to maintain a constant normal level for which the normal function of the kidney is responsible When, however, the creatinine of the urine is examined, it is found that during pregnancy the amount eliminated in the course of the day is considerably more than that recorded for normal women This high creatinine value drops immediately after delivery to quantities that are almost identical with those reported for normal women The average for the pregnant months is 630 mg per twenty-four hours, and for the weeks following parturition, 340 mg

TABLE 5—*Summary of Complete Data*

	Antepartum by Months				Postpartum by Weeks						
	6	7	8	9	1	2	3	4	5	6	7
Inorganic phosphorus in blood	2.44	2.35	2.57	2.61	2.64	2.32	2.07	2.10	1.89	2.22	2.39
Calcium concentration in blood	11.29	11.33	11.62	11.14	11.09	10.87	10.51	11.44	11.66	11.18	11.58
Creatinine in blood	2.03	1.89	2.09	2.07	2.11	1.98	1.43	2.02	2.08	2.29	
Creatinine in urine	640	634	642	593	256	263	332	492	316	307	

CONCLUSION

It is hardly necessary to emphasize the fact that many difficulties surround the study of mineral metabolism, and that as a result we have relatively no trustworthy information about the subject It is certain that the minerals are essential to normal growth and nutrition, and one can easily appreciate the far greater importance these factors assume when the discussion concerns pregnancy

The formation of the fetus involves not only ordinary growth but also an enormous growth of bone tissue Calcium, together with phosphorus, is important in bone formation Calcium also plays a significant rôle in the coagulation of the blood, the contraction of muscle, the permeability of cells and the regulation of blood sugar The softening of the teeth and the concomitant tendency to decay during pregnancy may be due to the lack of sufficient calcium in the diet to supply both the fetus and the mother

⁸ Sherwin, C. P., and Killian, J. A. *Am J Obst & Gynec* 2:6 (July) 1921

The phosphorus is a constituent of all nuclear material, and with magnesium and calcium gives hardness to bone. Both of these materials, therefore, are intimately connected during gestation, and the fact that, despite the enormous drain on them, the mother is able to keep a normal level is both interesting and suggestive of more detailed studies.

The creatinine is a substance about which there has been considerable interest. Especially is this true of the creatinine of women. It is an index of endogenous protein metabolism, the amount of excretion varying per day and depending on the size of the individual, or rather of the protoplasmic mass. It is materially altered in physiologic crises, such as regeneration of tissues, fevers, wasting diseases, and the so-called premortal rise on prolonged fasting. For which reasons it has been considered of unusual significance during the period of the fetal growth.

In concluding, we might summarize as follows:

- 1 The calcium concentration of pregnant women during gestation was found to be normal, with a slight decrease immediately after parturition and a rise to high normal just before dismissal.

- 2 Pregnancy did not alter the phosphorus content of the blood of the group studied, nor was there any change during the postpartum period.

- 3 High normal concentrations of creatinine were found in the blood during the antepartum and the postpartum periods.

- 4 The output of creatinine in the urine was increased during the fetal formation but returned to normality immediately on parturition.

ARTERIOSCLEROSIS AND INCREASED BLOOD PRESSURE

EXPERIMENTAL PRODUCTION *

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AND

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There is a great diversity of opinion concerning the etiologic factors of increased blood pressure and arteriosclerosis. The frequent association of the two conditions is granted. Which precedes the other, and what precedes both, have been matters of much study and debate. Five theories regarding the etiology of arteriosclerosis and hypertension may be considered:

1 Mechanical-physical theory. A wearing out of the blood vessels as the result of the stress and strain of life.

2 Chemical or infectious poisons theory. These may be exogenous, as from nicotine, or endogenous, as in chronic bacterial infections, diabetes, gout and nephritis.

3 Metabolic theory. Poorly balanced diets with excess of protein or cholesterol, harmful but as yet undesignated end products of protein metabolism.

4 Predisposition of certain groups of persons to degeneration of blood vessels theory.

5 Disturbance of the acid-base balance theory. Such a disturbance in human subjects results from the continued eating of a diet high in protein foods. The urine from such a diet is frequently from 100 to 1,000 times as acid as the body fluids¹. It has been suggested that the continued passage of an excessively acid urine might in itself damage the kidneys and play some rôle in the production of a generalized arteriosclerosis.

* From the laboratories of the Potter Memorial Clinic of the Santa Barbara Cottage Hospital.

1 Sansum, W. D., Blatherwick, N. R., and Smith, F. The Use of Basic Diets in the Treatment of Nephritis, J. A. M. A. 81:883 (Sept. 15) 1923.

In a previous article² we have demonstrated the results of feeding experiments with rabbits which resulted in a considerable increase in blood pressure (fig 1). Varying degrees of arteriosclerosis, in addition to the increase in blood pressure, were produced in three groups of twelve animals on high protein diets. One group was fed an animal protein, liver, a second group, oat protein, and a third group, soy bean protein.

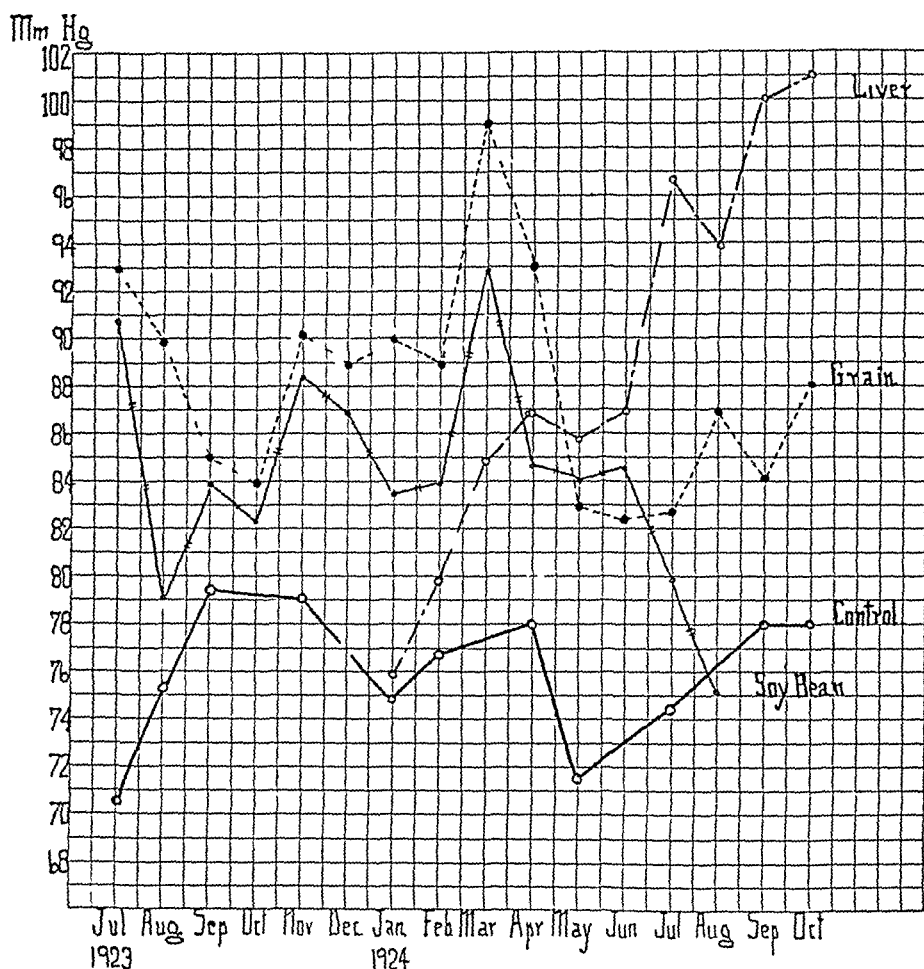


Fig 1—Blood pressure in four groups of animals each dot represents average of readings on the twelve animals in that group

This article is concerned with the pathologic aspect of this degenerative process, with the gross and microscopic relationship to human sclerosis, and with a consideration of the etiologic factors that may have played a rôle in producing these changes.

OBSERVATIONS

Liver Diet—The aortas of seven rabbits of a group of ten kept on a liver diet for from three to eleven months presented extensive arterio-

² Nuzum, F. R., Osborne, M., and Sansum, W. D. The Experimental Production of Hypertension, Arch Int Med 35:492 (April) 1925.

sclerosis Three rabbits on this diet for a period of less than three months did not present evidence of blood vessel change Grossly, the intima of the aorta presented raised yellow-white areas which in some instances involved the entire lumen of the vessel and extended in patches from the root to its iliac bifurcation In one instance the pulmonary artery also was involved Microscopically, this process of intimal change has been followed from an early swelling of the intercellular cement substance of the intima to a marked thickening with the deposition of calcium soap in considerable amounts In the later stages of intimal swelling, the elastic fibers become destroyed and the cellular structures are replaced by a homogeneous hyaline-like material It is in this hyaline

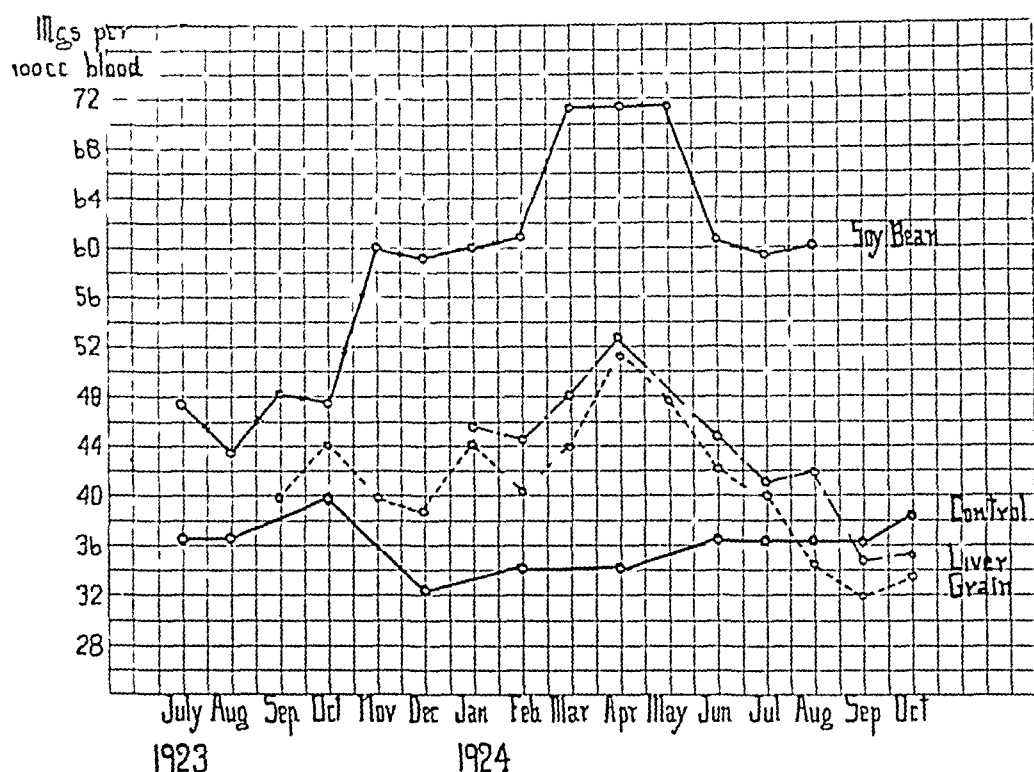


Fig 2—Nonprotein nitrogen of blood each dot represents average of twelve nonprotein nitrogen determinations of that group

substance that the calcium is found Not until the intimal changes have reached an advanced stage do the endothelial cells covering the intima break down In some instances of advanced change in the intima, these degenerative processes have extended by continuity into the media, but never extensively The intimal changes were particularly prone to occur about the mouths of the coronary and intercostal arteries, that is, at points of stress In each of the seven liver fed animals in which sclerosis of the aorta was found, sclerosis of one or both coronary arteries was likewise present to a considerable degree The microscopic picture of the coronary sclerosis was precisely like that of the aorta

There was no evidence of spontaneous (medial) sclerosis in any animal of the liver group. In spontaneous sclerosis the changes are confined to the media and consist of a necrosis of the smooth muscle cells and of a deposition of calcium in the necrotic areas. The overlying intima is not involved. On the frequency of this condition in rabbits there have been many reports, but nearly all lack a careful study of the histology and the writers have therefore failed to recognize these two types of sclerosis. The literature on this question has recently been summarized by Newburgh and Clarkson³

The blood pressures in this group were higher than in any other and were highest in those animals in which the sclerosis was most marked. In each of these animals there also was definite evidence of kidney

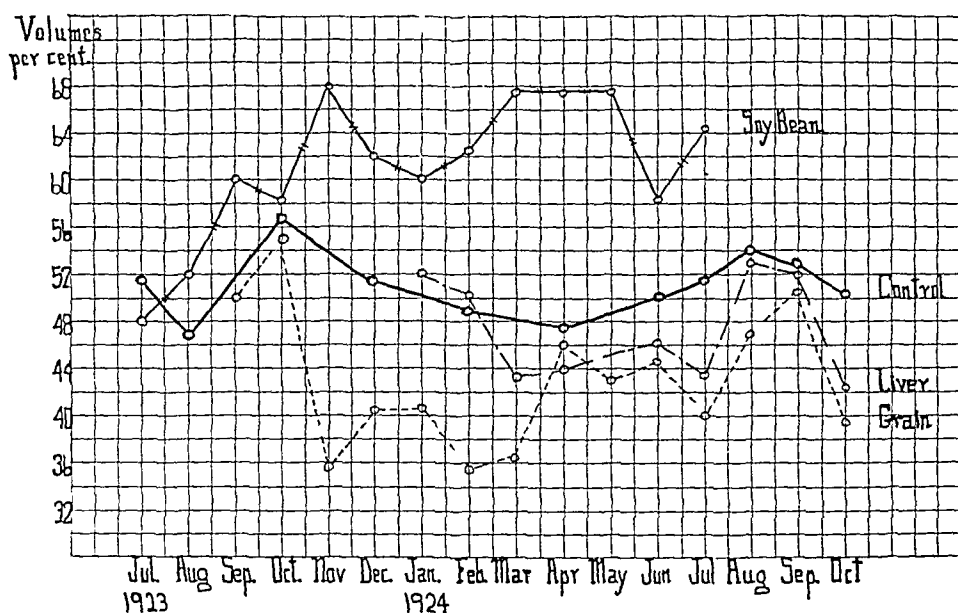


Fig 3—Carbon dioxide of blood each dot represents average of carbon dioxide determinations on blood of the twelve animals in that group

injury as shown by the presence of albumin and casts in the urine and by an increase of nonprotein nitrogen and urea nitrogen in the blood. The urines of these animals were decidedly acid, the p_H ranging from 5.0 to 7.0. The carbon dioxide of the blood serum was decreased.

Grain Diet—The aortas of seven of eleven animals kept on an oat diet for two years (with the addition of green vegetables at stated times) presented marked arteriosclerosis. These changes were most pronounced in the arch and extended down into the abdominal aorta as isolated scattered patches. The largest areas of intimal thickening in this group

3 Newburgh, L. H., and Clarkson, Sarah. The Production of Arteriosclerosis in Rabbits by Feeding Diets Rich in Meat, Arch Int Med **31** 653 (May) 1923

were 10 by 8 mm and 15 by 3 mm. These patches, as in the liver group, were especially to be found about the mouths of the intercostal vessels. The coronary arteries contained areas of sclerosis in three of the seven instances that presented aortic changes.

Spontaneous or medial sclerosis was present in three of the seven animals that had an intimal sclerosis. This type of change presents grossly a thinning of the wall of the aorta in contrast to a thickening such as occurs in arteriosclerosis. The intima is depressed over these thinned areas but is intact. On section, calcification, confined to the media, is present. This calcification may extend for considerable distances along the vessel. Its width was usually not more than from 3 to 4 mm. In none of our instances was the intima involved.

In one instance a group of cartilage cells was found beneath an area of medial calcification. This has been seen before but seems to be rare.



Fig 4—Extensive sclerosis of intima of aorta of rabbit that had been on a liver protein diet for fifteen months.

The most pronounced arteriosclerosis was found in the animals that had been on the grain diet for the longest time (two years). It was these animals, also, that had the most marked increase in blood pressure, the maximum pressures ranging between 90 and 100 mm of mercury, whereas the pressures of these animals at the beginning of the experiment and the pressures of the control animals averaged 74 mm. The kidneys of these grain fed animals that presented areas of sclerosis and increased blood pressure likewise gave evidence of injury. Albumin and casts were present in the urine after the sixth month of the experiment. The urine was acid, the p_H ranging from 6.0 to 6.8. The carbon dioxide of the blood serum was decreased. The nonprotein nitrogen and the urea nitrogen of the blood were increased.

Soy Bean—A third group of twelve animals was kept on a diet of ground soy beans for two years. (At weekly intervals greens were

added to this diet to prevent deficiency diseases) The protein in this diet averaged 36 per cent and was of the vegetable type It was given because it produces an alkaline urine in contrast to the acid urines that the other two groups of protein produce The p_H of the urine of this soy bean group averaged 9.0, which is high even for the rabbit whose urine on a herbivorous diet does not exceed a p_H of 8.0 Not one of the twelve animals in this group presented true arteriosclerosis Three presented areas of spontaneous or medial sclerosis One of the animals presenting this type of sclerosis, which began just above the aortic cusps and spread up over the arch almost totally covering the transverse and descending portions and extending on down along the entire length of the aorta, developed an infected wound of the neck during the thirteenth

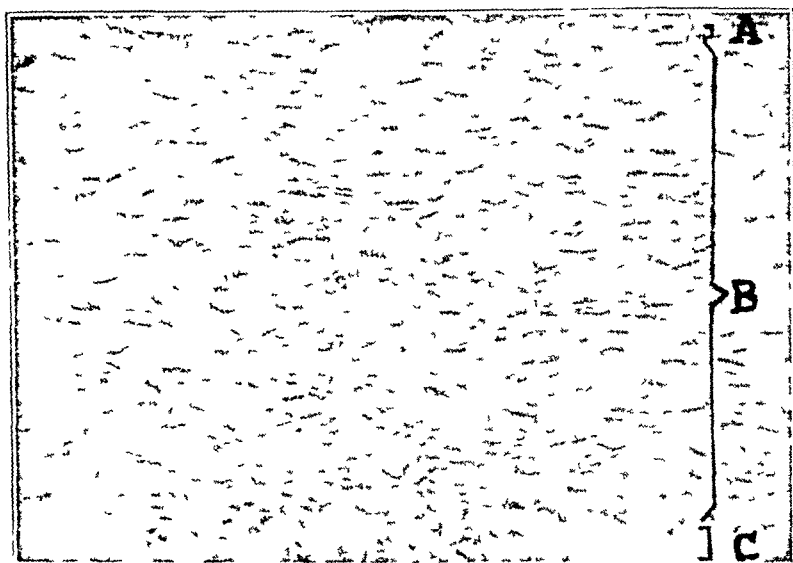


Fig 5—Section of normal rabbit aorta A, intima, B, media, and C, adventitia

month of the experiment and was killed on the seventeenth month because of its poor condition The relation of this infection to the medial sclerosis must be considered The blood pressure of this animal did not exceed 90 mm of mercury at the maximum Clinically, the kidneys did not give evidence of damage There was no increase of the nonprotein nitrogen and the urea nitrogen of the blood

Controls—A group of twelve control animals was kept under the same living conditions as the foregoing groups and fed on a mixed diet of oats, alfalfa and greens At the end of the two year period they were killed No sclerosis of either type was found in either aorta or coronary arteries The blood pressure averaged 74 mm, which is normal The urine did not give evidence of kidney damage The non-protein nitrogen and urea nitrogen of the blood remained normal

COMMENT

The term arteriosclerosis has been employed here because of its general use, although Marchand's term, atherosclerosis, more accurately describes the pathologic condition as worked out by many investigators.

The earliest changes visible at necropsy consist of small raised yellow specks in the intima. These are due to a deposition of fat droplets containing cholesterol esters in the extracellular cement substance of the intima, secondary to a loosening and swelling of this cement substance.⁴ The combined changes result in a swelling or thickening of the intima.

These early changes may regress or may progress. In the latter event, the cement substance fuses into a hyaline mass. The surrounding connective tissue is stimulated by this process and these areas become

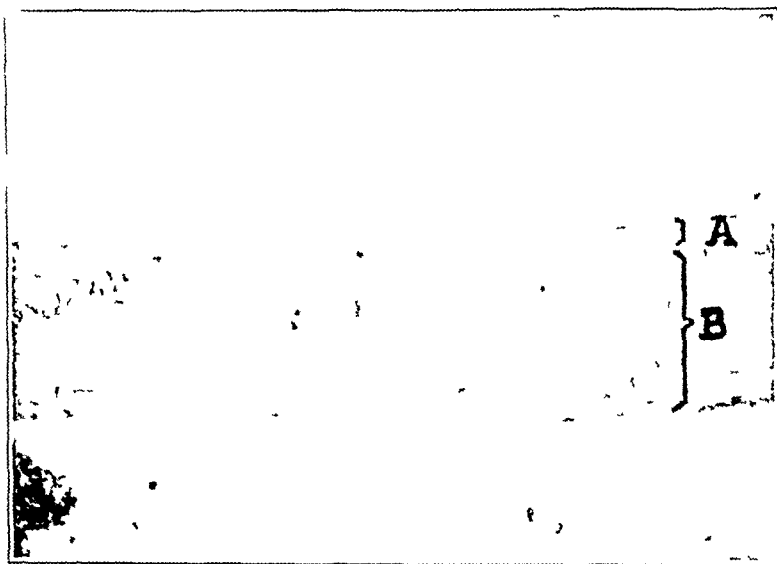


Fig 6—Early change limited to intima of aorta and consisting of swelling of intercellular cement substance and beginning deposition of hyaline material *A*, intima, and *B*, media

covered with newly formed connective tissue. This new connective tissue swells and a deposition of hyaline material again occurs. Thus, layer is added to layer. In this area the deposition of fatty substances continues until the tissue cells and intracellular substance become so overloaded with fatty material that necrosis occurs. The cholesterol esters split up. Cholesterol is freed and precipitates out as crystals. The liberated fatty acids form soaps, the calcium soap leading to the incrustation and calcification that characterize the atheromatous ulcer.

Many of our animals presented arteriosclerotic changes, the counterpart of human sclerosis, as described above (figs 5 to 10). In the aortas of these animals the earliest lesion was found to be primarily the

4 Aschoff, Ludwig. Arteriosclerosis, New York, Paul B. Hoeber, 1924.

swelling of the intercellular cement substance. This was followed by a deposition of fat substances, of hyaline material and finally of calcium soaps. These changes occurred with greatest frequency in those animals on a 20 per cent liver protein diet in which the most marked increase in blood pressure was obtained, whose kidneys gave evidence of a nephritis, and whose blood gave evidence of retained end products of protein metabolism. The urines of these animals were continuously acid.

The factors responsible for the increased blood pressure and the arteriosclerosis may have been excessive protein diet, excess of cholesterol in the diet, or excessively acid urine over a long period of time.

The question as to whether increased blood pressure is responsible for degenerative changes in the kidneys and blood vessels, whether the process is reversed, or whether both these changes are dependent on some

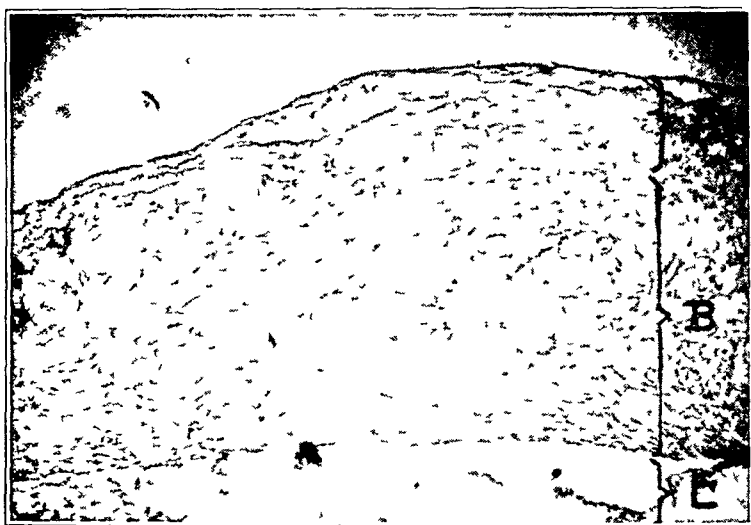


Fig 7—More marked intimal change, a further step in the process of sclerosis
A, intima, B, media, and C, adventitia

primary etiologic factor, is answered in part by our results. The highest experimental blood pressures were obtained in animals that at necropsy presented the most extensive sclerosis of the aorta. It is also true that the highest blood pressures and most extensive blood vessel changes were obtained in the group of animals on the diet that had the most acid urines (the liver group).

Whether the changes were dependent on excessive cholesterol or excessive protein is elucidated by our experiments. The conclusion of German investigators, particularly Schmidtman,⁵ Antischkow,⁶

5 Schmidtman, M. Experimentelle Studien zur Pathogenese der Arteriosklerose, *Virchows Arch f path Anat* **237** 1, 1922

6 Antischkow, N. Ueber die experimentelle Atherosklerose der Aorta beim Meerschweinchen, *Beitr z path Anat u z allg Pathol* **70** 265, 1922

Monckeberg,⁷ Schoenheimer,⁸ Aschoff and others, was that cholesterol is responsible for the arteriosclerosis that occurs in rabbits, guinea-pigs and cats, which are the only experimental animals in which these changes have been produced to date. The diets of these animals have contained considerable amounts of cholesterol or of cholesterol and neutral fats. When the latter are added, the resulting sclerosis seems more pronounced than when the same amount of cholesterol alone is given. In support of this contention, the findings of Kon are cited. He was unable to produce arteriosclerosis in rabbits fed a cholesterol free liver diet. Antischkow sums up the situation by saying, "Without cholesterol, no sclerosis." Newbough,³ as far as we can find, is the only investigator to raise an objection to this conclusion. As a result of feeding high protein diets he obtained well defined arteriosclerosis. Since his diets

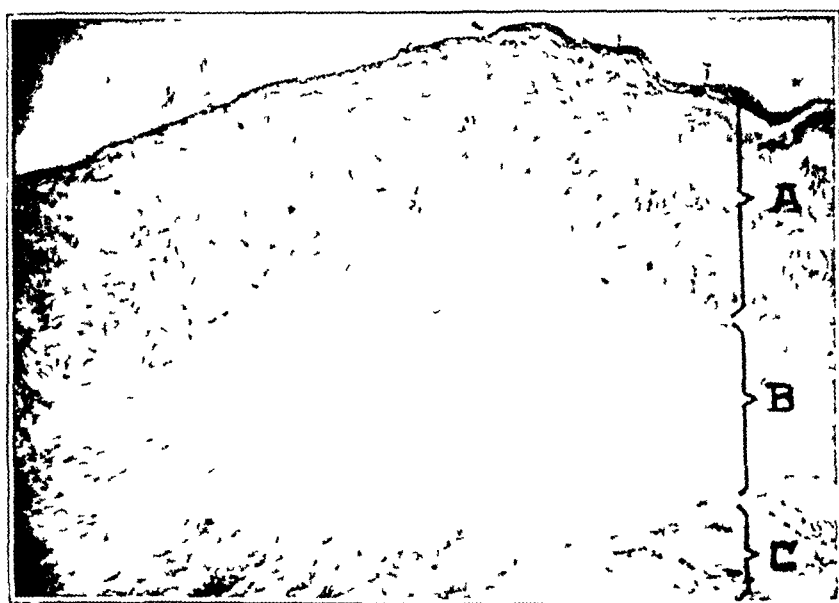


Fig 8—Marked thickening of intima, the result of arterial sclerotic degenerative changes. A, intima, B, media, and C, adventitia.

contained considerably smaller amounts of cholesterol than the amounts that are held necessary to produce experimental arteriosclerosis, he believes that the high protein factor is responsible for this degenerative change.

The amount of cholesterol in our liver diet will be made a matter of further study. Our grain diet, however, contained no cholesterol and yet seven of eleven animals developed a well defined and extensive arteriosclerosis. In this instance the increased blood pressure, the diet of high protein or the acid urines resulting from the ingestion of the protein

⁷ Monckeberg, J. G. Arteriosclerose, *Klin Wchnschr* **3** 1473 (Aug 12) 1924.

⁸ Schoenheimer, R. Ueber die experimentelle Cholesterin-Krankheit der Kaninchen, *Virchows Arch f path Anat* **1**:249-250, 1924.

diet must have been responsible for the sclerosis. We find that Newburgh's contention is just, that cholesterol is not necessary to the experimental production of arteriosclerosis, and that high protein diets may produce this change.

We attempted to determine whether the factor of disturbed acid-base balance as expressed by the long continued secretion of excessively acid urine might in itself be responsible for the increased blood pressure and the degenerative blood vessel changes. To this end, the high protein (36 per cent) soy bean diet was given. The vegetable protein resulted in the excretion of a urine whose p_H held around 9.0. The carbon dioxide of the blood serum averaged almost twice as high, 59 per cent by volume as against the control animals, 30 per cent by volume. While clinical evidence of kidney damage and an increase in

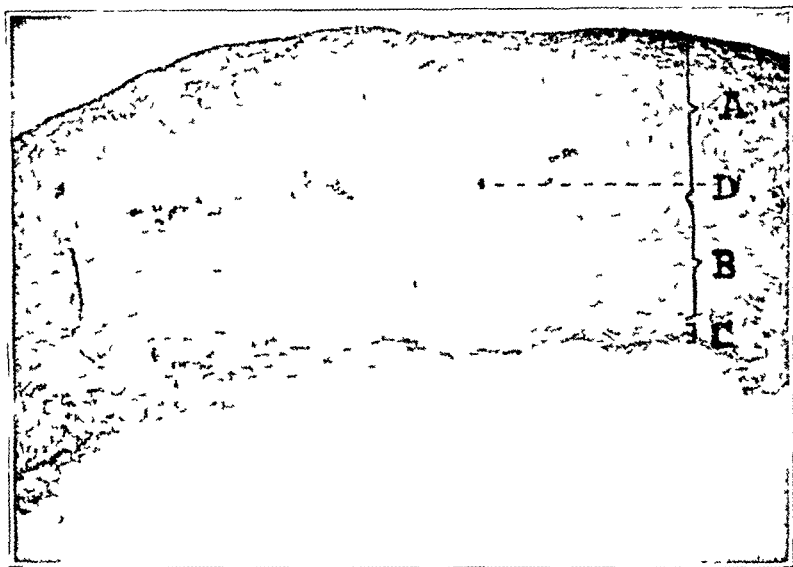


Fig 9—Early deposition of calcium in arterial sclerotic area. A, intima, B, media, C, adventitia, and D, calcium deposits.

the blood pressure did occur, yet no instance of intimal arteriosclerosis was found in any of the twelve animals of this group. One would expect kidney damage from the long continued alkalosis that resulted from the soy bean diet. Fischer⁹ has shown that excessive alkali is capable of producing kidney injury. Henderson, Palmer and Newburgh¹⁰ have drawn the same conclusion. Our experiments show clearly that a long continued disturbance of the acid-base balance of rabbits on the alkaline side is capable of causing a moderate hypertension and of causing kidney damage, but that it does not produce arterio-

9 Fischer, M. *Edema and Nephritis*, New York, John Wiley & Sons, 1915.

10 Henderson, L. J., Palmer, W. W., and Newburgh, L. H. *The Swelling of Colloids and Hydrogen Ion Concentration*, *J. Pharm. & Exper. Therap.* 5:449, 1914.

sclerosis The absence of arteriosclerosis may have been due to the fact that the blood pressure was not sufficiently increased in height or long enough maintained to produce this change

The occurrence of sclerosis of the vessels in the eye grounds was sought for in the animals of the various groups No changes were noted The spreading out of the optic nerve over the retina of the rabbit eye makes the detection of blood vessels difficult A marked arcus senilis occurred in each eye of a female rabbit in the liver group The occurrence of this condition was noted by Schoenheimer as occurring in female rabbits only, on a high cholesterol diet

The presence of arteriosclerosis in vessels other than the aorta has been found particularly by German investigators using high cholesterol diets The arteries of the spleen, kidneys, liver and lungs have been

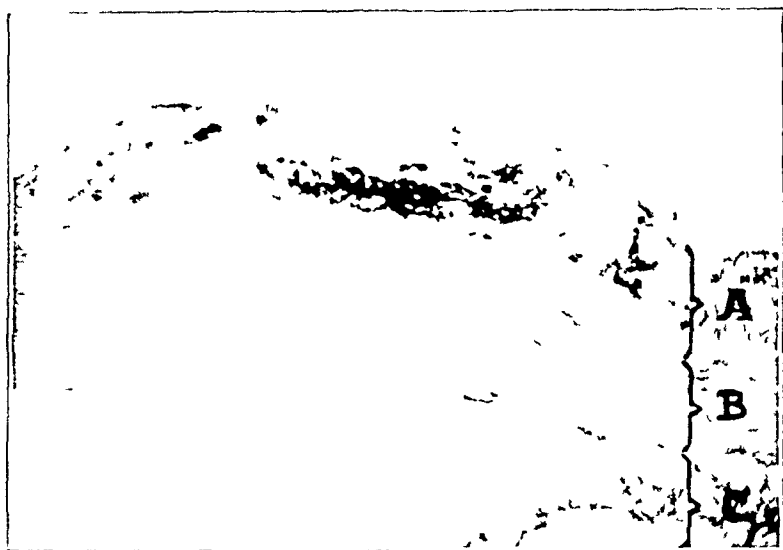


Fig 10—More extensive calcium deposits in an arterial sclerotic plaque of aorta from rabbit on a liver diet for sixteen months A, intima, B, media, and C, adventitia

affected In our groups, changes in these arteries were slight The coronary arteries, however, were frequently and extensively involved The swelling here occasionally almost occluded the lumen of these vessels This occurred most frequently in the left coronary artery In the same animals the blood pressures were the highest that we obtained and the thickness of the muscle and of the left ventricular wall was greater than in the control group The arteriosclerosis was frequently seen to involve the small vessels in the myocardium

The presence of fat was sought for in the myocardium, liver and kidneys of the animals that presented the sclerotic changes The livers of the liver diet group contained considerable amounts of lipid material as demonstrated by the fat stain sudan III The fat was present as fine dustlike particles and as larger droplets in the parenchymal cells of the

periphery of the lobule and in many instances extended well in toward the central vein. There was also easily demonstrable fat in the walls of the smaller arteries of the myocardium and scattered through the muscle cells themselves. In some instances the papillary muscles contained striking amounts of fat.

The stainable lipoid material in the livers, kidneys and myocardium of the grain and soy bean groups of animals was little, if any, greater than in the control group. This might be expected, since the diets of the latter groups contained no cholesterol.

Schoenheimer noted increased amounts of stainable lipoid in the hearts of all animals fed on a cholesterol diet for 100 days or longer. The fat occurred as fine striations and netlike structures involving both the papillary muscles and the walls of the ventricles. He concluded that these changes simulated Tigerung in man. He also noted thickening of the walls of the ventricles in the animals that had a marked arteriosclerosis of the coronary arteries. Our group of animals fed on a liver high protein diet presented changes coinciding with his.

SUMMARY

Four groups of factors have been outlined by numerous investigators as of etiologic importance in the production of arteriosclerosis and increased blood pressure.

To these a fifth group has more recently been added, i. e., a disturbance of the acid-base balance resulting in the excretion of excessively acid urines. This disturbance of balance has been produced by high protein diets both in man and in experimental animals. The dietary of the American people, with its excess of meat, cereals and bread, is of this acid type.

By feeding various excessive protein diets to experimental animals for periods as long as two years, we have obtained increased blood pressures. The animals in which the most marked increase of blood pressures were obtained presented extensive arteriosclerosis of the aorta and in many instances of the coronary arteries. Evidence of kidney damage was also obtained, as demonstrated by chemical studies of the blood and of the urine.

The histology of arteriosclerosis in rabbits is similar to that of human arteriosclerosis.

Spontaneous sclerosis in rabbits has an absolutely different histologic picture.

Our experiments demonstrate that increased blood pressure and arteriosclerosis can be produced without an increase of cholesterol in the diet.

Excessive amounts of fat were found in the liver and myocardium of animals whose diet was high in cholesterol.

DIAGNOSIS OF PULMONARY NEOPLASM*

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NEW YORK

There appears to have been a striking increase in the number of cases of cancer of the lung during recent years in America and Europe. That this increase is not altogether the result of greater precision in diagnosis is evident when we consider that not only clinicians have noted it, but also pathologists have reported to this effect. Douglass Symmers has observed this increase in the pathologic laboratories of the Bellevue Hospital in New York, and Hampeln,¹ Staehelin,² Assmann,³ Berblinger,⁴ Holzer,⁵ Heilmann,⁶ Kikuth,⁷ and others in Europe have published statistics to this effect. The problem to be cleared up by those engaged in cancer research is whether this goes hand in hand with the increase in visceral cancer recently observed in civilized countries or there is some special etiologic factor operative in the case of the lungs, such as dust in modern industrial centers, as noted by Hampeln,¹ Heilmann,⁶ and others, and the influenza epidemic, which left in its trail numerous injured lungs.⁸

In this article we deal with the clinical aspects of sixty cases of primary malignant disease of the bronchi, lung and pleura in Montefiore Hospital during the last ten years. In thirty-six, necropsies were obtained. We found that contrary to the prevailing opinion in clinical circles, the diagnosis of this disease can be made during life in the majority of cases.

* From the tuberculosis division of the Montefiore Hospital and the Bedford Hills Sanatorium for Incipient Tuberculosis.

1 Hampeln. Zur Symptomatologie und Diagnose der primären malignen Lungentumoren, *Mitt a d Grenzgeb d Med u Chir* **31** 672, 1919.

2 Staehelin, R. Zunahme des primären Lungenkrebses, *Klin Wchnschr* **4** 1853, 1925.

3 Assmann, H. Zur Frage der Pathogenese und zur Klinik des Bronchialkrebses, *Med Klin* **20** 1757, 1796, 1924.

4 Berblinger, W. Die Zunahme des primären Lungenkrebses, *Klin Wchnschr* **4** 913 (May 7) 1925.

5 Holzer, H. Zur Frage der Häufigkeit des Bronchialkrebses, *Med Klin* **21** 1235, 1925.

6 Heilmann, P. Ueber die Zunahme des primären Lungenkarzinoms, *Virchows Arch f path Anat* **255** 549, 1925.

7 Kikuth, W. Ueber Lungenkarzinom, *Virchows Arch f path Anat* **255** 107, 1925.

8 Moise, T. S. Carcinoma of the Lung, *Arch Int Med* **28** 733 (Dec.) 1921.
Assmann (Footnote 3) Berblinger (Footnote 4)

The average age of these sixty patients was 55 years. The age period distribution was as follows:

Below 40	8, or 13.33 per cent
From 40 to 50	11, or 18.34 per cent
From 50 to 60	23, or 38.33 per cent
From 60 to 70	14, or 23.33 per cent
70 and over	4, or 6.67 per cent

The majority of cases occurred in persons between 40 and 70 years of age, which is the age distribution of cancer in general. The youngest of our hospital patients was 31, and the oldest 84, but I have seen two cases in persons 18 and 21, respectively. There have been reported even younger persons with malignant disease of the lung.

Of our patients forty-four, or 73.3 per cent, were men and sixteen, or 26.6 per cent, were women. Most other writers have found that men predominate. Among the 374 cases compiled by Adler⁹ 71.9 per cent were in men.

NECROPSY FINDINGS

Necropsies were obtained in thirty-six cases and superficial glands were excised for microscopic study in eight. Of these, we found that thirty-five were carcinomas and only one a spindle cell sarcoma. The great predominance of carcinoma of the lung has been noted by nearly all who have reported on large series of cases. Only Rolleston and Trevor¹⁰ state that most pulmonary tumors are sarcomas, but this is contrary to all other observations, and it would seem that Barron¹¹ is right in assuming some confusion on their part. Though it has been stated that cancer is considerably more frequent in the right lung and theoretical explanations have been advanced for this supposed phenomenon, in our series the left lung was the seat of the tumor in 56.6 per cent of the cases. There was no predominance of either side in the 374 cases compiled by Adler⁹.

The macroscopic picture of the carcinomatous lung is exceedingly varied, owing not only to the variety of forms in which the tumor itself may grow but even more to secondary nutritive and circulatory disturbances in the tumor tissue and the mechanical consequences of compression by the growing tumor, to these may be added changes due to infection of the growth with any of the pyogenic microorganisms, which is not infrequent.

As regards their macroscopic appearance, our cases may be divided into four groups:

⁹ Adler, I. *Primary Malignant Growths of the Lungs and Bronchi*, New York, 1912.

¹⁰ Rolleston and Trevor. *Brit. M. J.* **1**: 361, 1903.

¹¹ Barron, M. *Carcinoma of the Lung*, *Arch. Surg.* **4**: 624 (May) 1922.

1 The most common picture is that of an irregularly delimited yellowish or grayish mass in the vicinity of the hilum, infiltrating the parenchyma more peripherally, usually of the hilum of the upper lobe. On section of the tumor one can often discover the still patent lumen of the bronchus from which the tumor took its origin.

2 Another, not nearly so common, finding is that of a coarsely nodular mass embedded in the parenchyma of any part of the lung with much better defined outlines than the tumors of the first mentioned group.

3 A further rare form is a diffuse carcinomatous infiltration of one or more lobes, whose appearance presents great similarity to that of an extensive caseous pneumonia.



Fig 1—Metastatic deposits in lungs from carcinoma of stomach, each deposit is clearly seen.

4 Three of our cases were the much disputed “endothelioma of the pleura,” the lung being covered by a thick nodular sheet. The so-called primary miliary carcinosis, though it undoubtedly occurs, was not observed in our series, but we have seen it many times in cases of secondary cancer of the lung (fig 3). Closely neighboring on the primary growth are often seen metastases to the pulmonary parenchyma. Extensions from the primary growth along the peribronchial and, not so commonly, the perivascular lymphatics may form a prominent feature. In some cases the eye is first struck, when the breast plate is removed, by peculiar patterns outlined on the pleural surface through the permeation of the subpleural lymphatics by carcinoma cells, known as lymphangitis carcinomatosa.

The relations of the growth to the bronchus of origin are of primary interest in explaining the physical signs on which we lay so much stress in the diagnosis of these cases. Rather uncommonly the tumor grows along the bronchial wall forming an eccentric envelopment, thus con-

verting the bronchus into a thick walled tube. But as a rule there is extreme narrowing. This may be due to an annular growth gradually diminishing the lumen, or to complete obturation by a ball-like mass of tumor tissue.

Secondary changes in the tumor itself and reactive phenomena on the part of the adjacent lung tissue form an integral part of the picture. The tumor may proliferate so rapidly as to outgrow its blood supply.

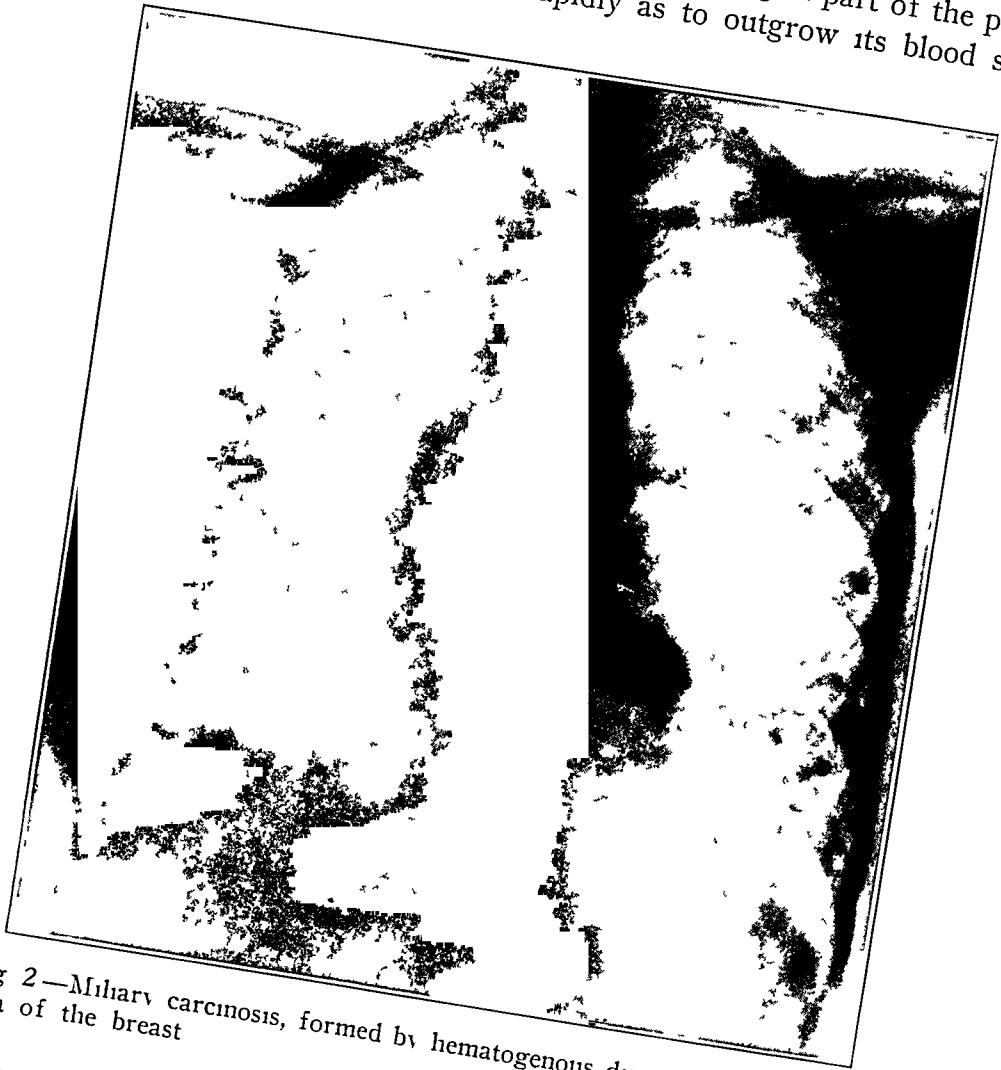


Fig 2—Miliary carcinosis, formed by hematogenous dissemination from a carcinoma of the breast

with consequent necrosis of the central portions. The necrotic tissue may be evacuated through the bronchus with resulting cavity formation. Very much as in tuberculosis, these cavities may become secondarily infected and at necropsy are often found full of pus and lined with a pyogenic membrane. Aneurysmal dilatations of vessels may be found projecting into the cavity. There may be many discrete cavities, or one large one. In two cases there was one large cavity with a thin wall of tumor tissue (figs 21 and 22) recognizable as such only on microscopic

examination, without any metastases either in the lung or any other organ. In four cases an entire lobe was thus destroyed. While every form of bronchial carcinoma may bleed, thus producing streaky sputum, those with necrosis and cavity formation may be accompanied by copious and even fatal hemorrhages when a large vessel is eroded. Usually there are considerable areas of chronic indurative pneumonia surrounding the neoplasm, but there are cases in which the adjacent lung remains quite normal, as was the case with the large cavities just mentioned (figs 19 to 21). There may be quite extensive atelectasis in the



Fig 3

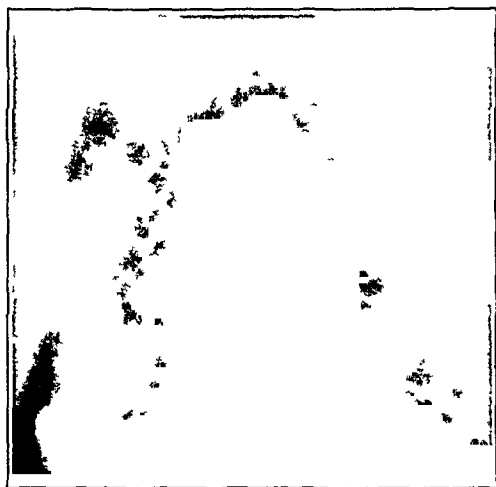


Fig 4

Fig 3—Primary carcinoma of left lung, cloudiness at periphery beyond the limits of the solid tumor, due to atelectasis, and also elevation of diaphragm should be noted

Fig 4—Primary carcinoma of right lung, upper part of tumor broken down

portions of the lung whose bronchial supply has been impaired or obliterated (figs 3, 4 and 11). The frequent serous, sanguineous and purulent pleural effusion accompanying lung tumor are discussed later on.

The histology and more the histogenesis of pulmonary carcinoma have been moot questions for years, and as yet complete unanimity has not been attained. The reasons for the great difficulty in interpreting the cytology of these tumors in terms of their histogenesis are evident when one considers that while the epithelium lining the bronchopulmonary system is continuous from the trachea to the alveoli, gradual changes in the morphology of the lining epithelial cells occur in the transition from the ciliated columnar cells of the larger bronchi, through cuboidal forms, to the flat alveolar epithelium. Moreover, the bronchial mucous glands consist merely of modified bronchial epithelium

Instances of metaplasia of the columnar cells lining the larger bronchi into squamous cells are very common as a result of inflammatory processes. From these considerations it is evident how unsafe it is to draw conclusions as to the histogenesis of the tumor from morphologic observations. However, it is generally agreed that pulmonary carcinoma is almost synonymous with bronchial carcinoma, that neoplasms originating from the alveolar epithelium are rare, though they probably occur. A certain group of these tumors unquestionably originates from the bronchial mucous glands, as was long ago demonstrated by Langhans¹². Certain others seem to originate quite certainly from the ciliated columnar epithelium of the larger bronchi. Bearing in mind the difficulties just enumerated, we will not attempt to classify the tumors of our series

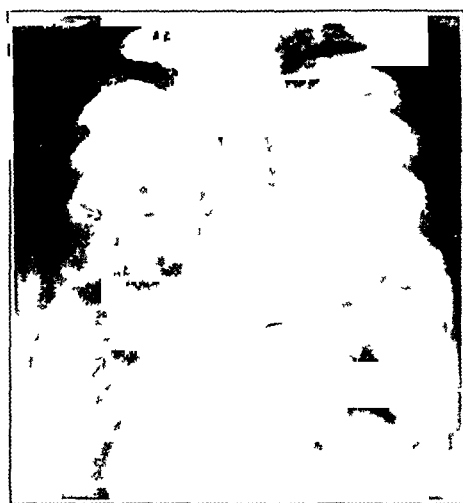


Fig 5—Primary carcinoma of the right lung extending along the lymphatics, in lymphangitis carcinomatosa

histogenetically, contenting ourselves with the mere statement that in twenty of the thirty-six carcinomas, the predominating type of cell was columnar and in most cases showed more or less tendency to the formation of glandlike figures, i. e., adenocarcinoma. In twelve cases the tumor was made up of squamous cells in which cornification with the formation of epithelial pearls, epithelioma, was to be discerned. Three belonged to the group ordinarily termed endothelioma of the pleura.

METASTASES

In nearly all cases of carcinoma of the lung other organs are involved, either by direct extension of the primary growth (mediastinal organs, chest wall) or metastasis. Widespread metastases may occur from small primary growths, but we have seen cases in which the tumor remained

¹² Langhans. Primärer Krebs d. Trachea u. Bronchien, Virchows Arch f. path. Anat. **53** 470 1871

in the lung for months to a fatal termination without any metastases at all. One point must be emphasized, and this has a clinical bearing. Clinically discernible metastases almost always occur late in the course of cancer of the lung, though there are striking exceptions, particularly as regards skeletal metastases. In primary sarcoma of the lung, on the contrary, metastases are usually early. Some patients with primary carcinoma of the lung go along for one or two years, in rare instances even longer, with the growth confined to its original seat in the lung. At the necropsy the opposite lung may be found free from neoplastic implantation, this was so in most of our cases. The thirty-six cases in which necropsies were performed showed the following metastases:

Regional lymph nodes	30
Distant lymph nodes	17
Lung (9 to opposite lung)	12
Liver	10
Suprarenals	8
Kidneys	6
Bones	2
Dura	2
Brain	2
Thyroid	1
Spleen	1
Pancreas	1
Rectum	1

In many cases the problem arises whether the growth discovered clinically in the lung is primary or secondary, i. e., a metastatic deposit from a tumor in some other organ which has escaped detection. Some, in fact, maintain that the vast majority of cancers of the lung are secondary to cancer of the esophagus, thyroid, prostate or suprarenals. In the cases reported here, a careful search was made to find the original site of the neoplasm, and when found in another organ, the case was excluded from this series. We must acknowledge that while we are satisfied that in all our cases the tumor was primary in the bronchi, lung or pleura, it is possible that some were in fact of the secondary type. In this connection it is important to mention that even after a careful necropsy this problem cannot be settled in every case. In several of our cases competent pathologists could not agree whether they should be considered primary or secondary. Of course the clinician is more liable to err in this respect than those who have opportunities to dissect the body.

CLINICAL FEATURES

The difficulties at attempts at diagnosis of primary cancer of the lung will be appreciated when we mention that 80 per cent of our patients were sent in with diagnoses of other diseases even though most were

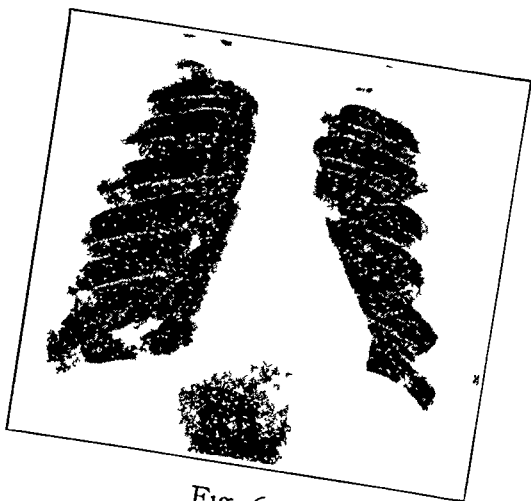


Fig 6

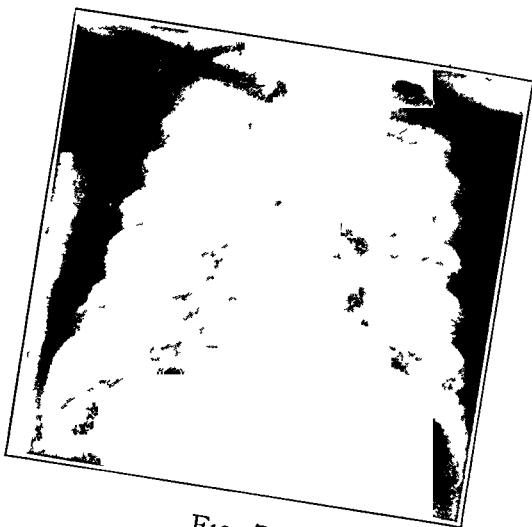


Fig 7

Fig 6—Hypernephroma, April 10, 1923, showing no involvement of lungs, physical examination indicated tumor in left base

Fig 7—Same patient as shown in figure 6, Sept 4, 1924, small tumor clearly shown near cardiac apex

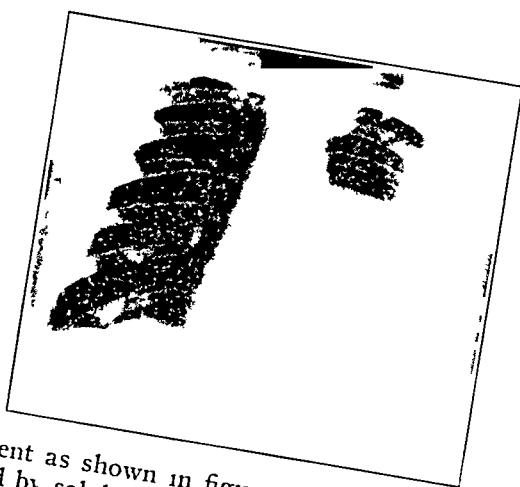


Fig 8—Same patient as shown in figures 6 and 7, Nov 13, 1924, lower half of left lung is replaced by solid tumor mass

observed in other hospitals before admission to Montefiore. This is not exceptional as can be seen from textbooks on medicine and monographs on diseases of the lungs. In most it is stated that the majority of cases are revealed only on the necropsy table. Sehart¹³ compiled from the literature 210 cases and of these only six were diagnosed during life. Adler's⁹ compilation shows similar results. Even with the most modern methods of diagnosis things have not improved to a desirable extent. Kikuth⁷ found that at the Eppendorf Hospital in Hamburg only 34 per cent of 246 cases were diagnosed during life, 11 per cent were suspected, and in 55 per cent diagnoses of other diseases were made. Likewise in the Basel clinic Staehelin² found that only in 30 per cent were correct diagnoses made during life, in 11 per cent cancer was suspected, in 3 per cent mediastinal tumor was diagnosed, and in 51 per cent diagnoses of other diseases were made.

It has, however, been our experience that cancer of the lung has a semeiology of its own and that the diagnosis offers no insuperable difficulties. When the symptomatology and physical signs are carefully gone into and properly interpreted the chances of error are no higher than in other chronic pulmonary diseases. While roentgen-ray examination and the study of the cytology of the sputum and pleural exudates are invaluable in many cases and mostly as corroborative evidence, the history, symptomatology and physical signs are most important. Relying mainly on the just mentioned criteria we only rarely miss a case.

SYMPTOMS

The onset is insidious in nearly all cases though many patients assert that some symptom, commonly cough, dyspnea, pain in the chest, or hemoptysis, has suddenly made its appearance. In four cases that I observed the patients stated that the onset was sudden with chill, fever, pain and cough, simulating pneumonia for which they were treated. It seems rational that these patients had small neoplastic formations in the bronchi which gave slight or no symptoms, and that the pneumonia was an accidental incident at that time. After recovery from the pneumonia the symptoms of cancer of the lung were more clearly defined. On the other hand the tumor may have been causally related with the origin of the pneumonia. Two patients maintained that the onset followed injury to the chest, and though several authors have mentioned traumatic cancer of the lung it would seem more rational to consider the injuries as mere coincidences. One patient stated that the first symptom he noted was hoarseness, but he had definite symptoms referable to the chest for months to which he paid no attention. Some patients had

13 Sehart. Beitrag zur Kenntnis des primären Lungencarcinoms, Inaugural Dissertation, Leipzig, 1904.

been suffering from chronic pulmonary or bronchial diseases, especially bronchitis, emphysema, bronchiectasis and even tuberculosis, and here the onset of the new disease was not marked by any striking changes in the symptomatology

In over 90 per cent of the cases cough appears to have been the first symptom. At first dry and hacking, it later on becomes productive of sputum which, as a rule, shows no characteristic traits. It is clear that when the tumor is of the parenchymatous type, or grows from the root of the lung into the parenchyma, the cough may be unproductive for a comparatively long time. In the cases in which the neoplasm grows within the lumen of, or plugs, a bronchus, or presses against the lower end of the trachea, especially at its bifurcation, the cough is paroxysmal, at times agonizing or emetic. In the later stages, when gangrene of the tumor is not uncommon, the amount of sputum may be enormous, at times malodorous.

Only exceptionally may the diagnosis be made from a study of the cytology of the sputum. In far advanced cases clumps of tumor tissue are expectorated at times and a microscopic examination of these clumps may help in the identification of the variety of neoplasm. We must emphasize, however, that individual cells are of little, if any, help in diagnosis because epithelial cells derived from the mucous lining of the respiratory tract appear in many catarrhal conditions as well as in tuberculosis. In some instances, as was first described by Lenhartz¹⁴ great numbers of large, spherical cells, loaded with fat granules are found and he considered them pathognomonic of cancer of the lung. But they may also be found in other respiratory diseases, as Lenhartz himself acknowledged. At all events, the cytology of the sputum has been of assistance to us in early diagnosis in exceedingly few instances only and then has been merely corroborative.

Bloody sputum may occur early in the disease, but this is exceptional. Later on it is quite common and 60 per cent of our patients had hemoptysis during the course of the disease. When the tumor begins to decay, the sputum is mixed with blood, and may present the appearance of raspberry juice or currant jelly, of which some writers have spoken. When superinfection occurs, or disintegration due to circulatory changes in the tumor mass takes place, copious, uncontrollable and at times fatal hemorrhages may result. Four of our patients succumbed to pulmonary hemorrhage.

Dyspnea is another early symptom. In fifty-six out of our sixty cases it was one of the earliest symptoms that urged the patient to seek medical advice. It is quite mild in the beginning but becomes severe and, in many cases, hard to bear, not even being relieved by rest in bed. In

14 Lenhartz, in Ebstein. *Handbuch d. prakt. Med.*, Ed 2, 1905, 4

persons of the cancer age dyspnea, to which cannot be attributed a cardiac origin secondary to a valvular lesion, hypertension or pulmonary emphysema, when combined with cough, pain in the chest and slight hemoptysis, should excite suspicion. Dyspnea is exceedingly rare in early chronic phthisis and remains rare as long as the lesion is not extensive and there is no complicating pleural effusion or a pneumothorax, miliary involvement of the lungs, toxic myocardial injury or cardiac displacement in cirrhotic phthisis. In cancer of the lung the dyspnea is to some degree due to infiltration of the peribronchial and perivascular lymph vessels by neoplastic cells, lymphangitis carcinomatosa, causing rigidity of the lung and compression of the alveoli. This very type of dyspnea is also seen in miliary carcinomatosis, which is almost always secondary. When the tumor is larger, the dyspnea is aggravated by plugging of a large bronchus rarely even of the trachea, the growth extending within the tube or compressing it from without. In several cases the dyspnea, bearable at first, suddenly became aggravated and proved fatal within a short time, indicating extension of the tumor in such a manner as to compress the trachea. In a case of this sort we found at the necropsy that the tumor in the left lung extended to the pleura, mediastinum and, through the pericardium, into the left auricle. In two others the tumor extended into the right ventricle, causing intense dyspnea and cyanosis of the entire body. Another curious phenomenon has been observed. The intensity of the dyspnea was more or less intermittent in many cases, indicating that the tumor which exerted pressure on a bronchus moved away to some degree because of mechanical factors. In one case in which pneumothorax was induced for diagnostic purposes the growth was at first seen on the roentgenogram clearly, but later on the shadow indicating the tumor disappeared behind the shadow of the mediastinum and made us suspect an incorrect diagnosis. At the necropsy, however, the growth was found.

Stridor is another symptom that some writers consider characteristic, but it was only rarely observed among our patients. It occurs mainly when the mediastinal glands are implicated by extension of the growth or by metastases compressing the trachea. It was encountered in only four of our cases and only shortly before the end. Pleural effusion, which, as we shall see later on, occurs in 50 per cent of cases, aggravates the dyspnea.

Cyanosis is seen early in about 50 per cent of cases. Various degrees may be observed, but it is most severe when the tumor grows in the direction of the superior vena cava compressing this vessel. Acrocyanosis, as well as clubbed fingers, have been observed in 25 per cent of cases. Clubbed fingers appearing in a patient of middle age should urge careful examination of the lungs for tumor.

In some cases, though few, the course of the disease is afebrile throughout. In the majority careful thermometry reveals a mild subfebrile temperature, not unlike that seen in tuberculosis. Superinfection with pyogenic micro-organisms produces pronounced fever, at times as high as 104 F, and when in addition there is pain in the chest and fetid sputum a diagnosis of abscess or gangrene of the lung is made. This was the diagnosis in five cases admitted to our service, and in one the abscess was actually operated on. Any type of fever may occur, continuous, remittent, intermittent and hectic. Profuse sweating is not uncommon and many patients complain of night sweats.

It is noteworthy that emaciation is not an early symptom of cancer of the lung—a fact already observed by Laennec¹⁵. Most of our patients



Fig 9

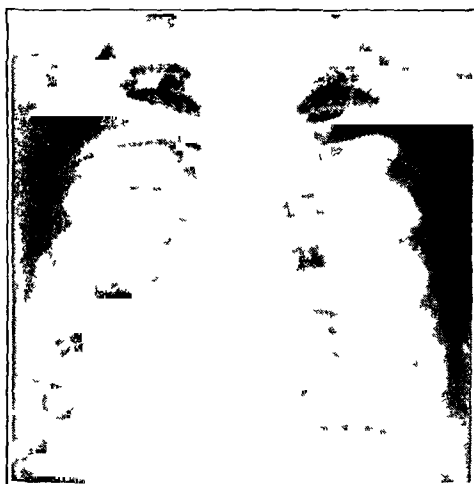


Fig 10

Fig 9—Practically normal appearance of patient, March 18, 1924, although physical examination showed probable tumor in lower lobe of left lung.

Fig 10—Same patient as shown in figure 9, May 30, 1924, tumor is clearly seen.

retained their weight for months, those treated for tuberculosis and urged to rest and eat excessively even gained in weight for some time. We have seen as much as 20 pounds (9 Kg) gained by patients within three or four months. In senile patients with otherwise latent cancer of the lung, the only striking symptom may be extreme emaciation, "senile marasmus."

Pain in the chest is one of the cardinal symptoms of *primary* cancer of the lung. In fact it was complained of by more than 90 per cent of our patients at an early period of the disease. It may be localized in

¹⁵ Laennec. *Traite de l'auscultation mediate*, Ed de la fac de med, Paris, 1878, p 510.

the region over the tumor, or radiate from the chest to the shoulder, or even to the finger tips. When it occurs in the left side and is due to pressure of metastatic deposits on the brachial plexus, it may, together with the dyspnea, simulate stenocardia, hence, such patients are at times treated for "heart disease." The pain may be continuous, but more often it is paroxysmal, simulating so-called intercostal neuralgia for which it is often mistaken. Cutaneous hyperesthesia is common. In several cases under our observation the first symptom that brought the patient to the physician was pain over a localized area of the lumbar spine. We have not been convinced that this was invariably due to early metastasis into the lumbar vertebrae, as is often the case with mammary, prostatic or other varieties of carcinoma with a tendency to bone



Fig 11



Fig 12

Fig 11—Dec 7, 1922, solid mass in upper part of right lung, near the periphery, diagnosed tumor

Fig 12—Same patient as shown in figure 11, June 10, 1924, mass has disappeared, leaving sharply delineated shadow extending from hilum to periphery, indicating thickened interlobar fissure

metastasis. In fact, metastasis is a rather late phenomenon in primary carcinoma of the lung, as has already been stated. In some cases the radiation of the pain was toward the abdomen. One point must be emphasized. Pain is exceptional in secondary carcinoma of the lung, and when it occurs it points to primary neoplasm of the bronchi, lung or pleura.

The distant pressure symptoms, spoken of so much in textbooks, are only exceptionally observed in pulmonary neoplasms, though they are quite common in mediastinal growths. Inequality of the pupils was observed only in three cases of this series. Likewise dilatation of the superficial veins of the chest and arm is only rarely seen, while it occurs frequently in mediastinal tumors which, exerting pressure on the superior vena cava produce dilatation and at times thrombosis of the superficial veins of the chest, arm, neck and even the face. The jugular

vein may be seen dilated and pulsating strongly in rare instances. Pronounced, even ghastly cyanosis of the neck, face and arm also goes with mediastinal growths. When the collateral venous circulation is insufficient to overcome the obstruction, in addition to cyanosis edema of the neck, face and arm also results. When the innominate vein alone is compressed the cyanosis is unilateral. However, in purely bronchial or parenchymatous neoplasms these symptoms are rare. We have observed them only twice in our series to any notable degree.

Likewise, enlargement of the superficial glands is but rarely met with in the early stages of primary neoplasm of the lung, contrary to Hodgkin's disease and lymphosarcoma. In the terminal stages, the glands in the supraclavicular region and, at times, in the axilla may be felt as enlarged and hard masses. Now and then, we meet with cases in which enlarged and palpable glands can be made out, especially those between the heads of the sternomastoid. It requires careful palpation to feel these glands as small, hard nodules freely movable. In a case of sarcoma of the lung a large mass was seen above the clavicle when the patient exhaled strongly which disappeared down into the thorax during inspiration. In rare instances we noted the glands on the neck enlarged to a degree to be visible on inspection. But it must be emphasized that primary carcinoma only rarely manifests itself thus. Enlarged cervical glands are much more common in lymphosarcoma and malignant granuloma.

DIAGNOSIS

The diagnosis can be made in the vast majority of cases quite early and the site of the growth localized if we bear in mind that clinically the disease manifests itself in three forms:

- 1 The pulmonary form, simulating tuberculosis
- 2 The pleural form, simulating pleurisy, dry or with serous, sanguineous or purulent effusions
- 3 The excavating form, simulating abscess and gangrene of the lung

THE PULMONARY FORM

The insidious appearance of cough, streaky sputum, mild fever, hemoptysis, dyspnea and pain in the chest in a person over 35 years of age should suggest not only tuberculosis or cardiovascular disease but also the likelihood of neoplasm of the lung. At this period of life tuberculosis is most often an exacerbation of an old dormant lesion and there is consequently a history of previous attacks of cough, expectoration and fever. The physical signs indicate a bilaterally active lesion or an active lesion in one lung and a sclerotic lesion in its mate. In tuberculosis there is almost invariably tachycardia, in tumor it is exceptional. Dyspnea is very common in tumor and rare in early tuberculosis. Unless

there are actual signs of pleurisy, acute and annoying pain in the chest is not as a rule a clinical manifestation of early tuberculosis. Pain due to vascular or cardiac disease can usually be accounted for by signs of disease of the heart or aorta which are lacking in cancer of the lung.

PHYSICAL SIGNS

In our experience, physical exploration of the chest is more likely to indicate the location of the growth at an early stage than the roentgen rays. We have repeatedly localized tumors of the lung by percussion and auscultation when the roentgenograms were entirely negative or inconclusive. Figures 6 to 10 show two cases in which the diagnosis was thus made by auscultation and percussion weeks before the roentgen rays revealed the growths unequivocally on the films.

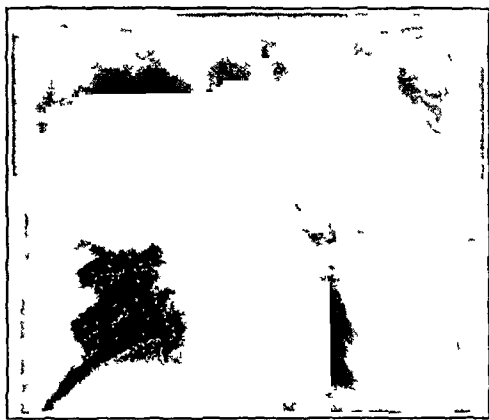


Fig. 13—Solid mass replacing upper half of right lung simulating tumor, clinical observation and bacteriologic findings, as well as miliary stipplings in right lower lobe indicated pulmonary tuberculosis.

The majority of primary tumors are bronchial and when quite small and growing within or near a bronchus often obliterate or compress the lumen of the tube, either by plugging it or compressing it from without. Atelectasis occurs in the area of lung tissue supplied by the plugged bronchus. The result is that usually we find a limited area of the chest wall which emits a *flat* note on percussion and the pleximeter finger feels a sense of resistance characteristic of flatness, as when a muscular limb or collection of fluid is percussed. In the majority of cases the bronchus supplying the upper lobe is thus affected, and flatness is elicited just below the clavicle near the sternum, or over the inner part of the supraclavicular fossa. Anteriorly the flat note extends under the sternum beyond the middle line.

Bearing in mind that a flat note is hardly ever elicited over a parenchymatous tuberculous lesion of an apex, and that the dullness never extends beyond the margin of the sternum, the significance of this sign becomes apparent. In tuberculosis the note is dull, at times even a

tympanic overtone is elicited, but never in tumor. In tumors of the lower lobes of the lung, which are less common than those in the upper lobes, obturation of the supplying bronchus produces somewhat similar signs. A flat note is elicited which may indicate tumor, thick pleura or a pleural effusion. In cases of inflammatory effusions a history of an acute onset with pain and fever will point to a diagnosis. When we deal with a thick pleura there is a long history of tuberculous disease, signs of a concomitant apical lesion, or a history of pneumonia, pleurisy or influenza with pleural effusion months or years prior to the onset of the present illness. In left sided tuberculous lesions because of pulmonary retraction, the heart is exposed, brought near the chest wall and may be seen pulsating in an abnormal place toward the axilla. This



Fig 14—Secondary carcinoma of left lung with pleural effusion, necropsy also revealed an active tuberculous lesion in right apex

is never seen in cases in which the impaired resonance is due to tumor, even though the mediastinum may be displaced toward the affected side. However, in tumors the flat note is in many cases elicited only over one aspect of the chest, while the other remains resonant. Flatness elicited only over part of the anterior aspect of the chest while the posterior remains resonant, or the reverse, is suggestive of tumor, provided of course an encapsulated effusion is excluded.

On auscultation we find feeble, at times completely absent breath sounds and no adventitious sounds over the limited area which was found flat on percussion. In tuberculosis of the upper lobe, even in cases in which caseation or fibrosis are extensive and produce a solid mass, as in figure 13, the note elicited on percussion is either impaired or dull but not flat, and changes in the character of the breath sounds are almost invariably heard, while any of the multifarious adventitious sounds characteristic of infiltration, consolidation, softening or excavation of lung tissue are audible. It may be said that flatness over a limited area, combined with feeble or absent breath sounds, suggests

tumor when found in a person of the cancer age giving a history of an insidious appearance of cough, dyspnea, hemoptysis and pain in the chest

Tuberculosis with extensive involvement of the lung to such a degree as to produce similar signs is commonly bilateral, signs of a lesion in

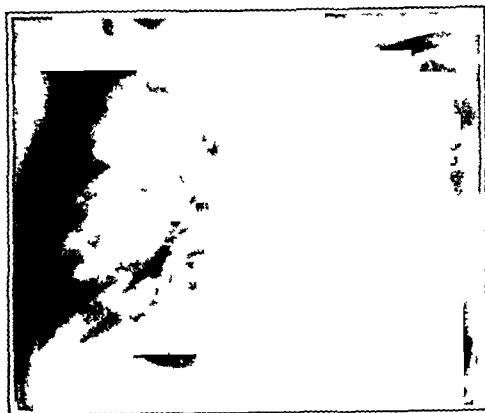


Fig 15—Primary carcinoma of left lung with multilobular effusion, some pouches containing serous, others purulent, and still other sanguineous fluid, a surgical operation had been performed

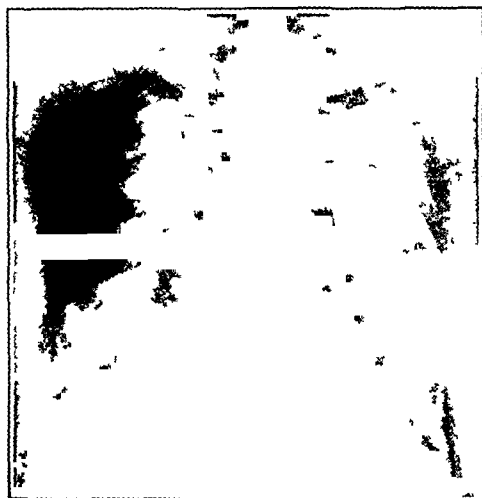


Fig 16—Interlobar effusion secondary to malignant tumor in right lung, subsequently the tumor invaded the entire right side of the chest

the opposite lung can almost invariably be made out. It is characteristic of primary pulmonary neoplasms that the tumor remains for a long time in one lung while the other continues free from demonstrable pathologic changes. This point is even more emphatically determined by a good roentgenogram. Our illustrations clearly show that the lesions are nearly all unilateral and when these are compared with roentgenograms of advanced tuberculosis the contrast is striking.

In cases in which the tumor advances along the peribronchial lymphatics it may act as a conductor of the sounds in the air tubes and the result is that on auscultation we hear tubular or even amphoric sounds. This sound has been called *cornage* by Behier¹⁶. It is usually heard near the sternum or in the interscapular space, while similar breath sounds in cases of tuberculous excavations are heard most commonly in the mammillary region, now and then as far out as the axilla.



Fig 17—Primary tumor of right lung in patient who had symptoms of gangrene



Fig 18—Round cell sarcoma primary in the mediastinum, invading the lung, the sputum was positive for tubercle bacilli. At necropsy chronic ulcerative tuberculosis was found in addition to the sarcoma.

above the third rib anteriorly and over the supraspinous fossa posteriorly, the percussion note is dull or even tympanitic, while in tumor it is flat.

It was stated above that the cytologic study of the sputum has been only exceptionally of diagnostic value. Of course, it is important that, despite the extent of the lesion, no tubercle bacilli are discovered. But

16 Behier. *Hopitaux de la Pétrie, Gaz. d. Hôp.* 45 177, 1867.

we have had four cases in which tubercle bacilli were found in the sputum and the necropsy confirmed the diagnosis of the coexistence of cancer and tuberculosis of the lung. Indeed, in cases in which the symptoms and signs enumerated above are clear cut, the discovery of tubercle bacilli in the sputum does not deter us from making a diagnosis of neoplasm of the lung.

ROENTGEN-RAY FINDINGS

Roentgenography, of course, is of decisive diagnostic import in many cases, but often the pictures are misleading, especially in the early stage of the disease. It is now quite widely recognized that the roentgen rays fail in many cases to clear up the diagnosis. Barjon¹⁷ insists that cooperation between the roentgenologist and the clinician is imperative "for there is no pathognomonic roentgen-ray picture of cancer of the pleura and lung." Assmann³ and Staehelin² speak to the same effect. Bryan¹⁸ reports frankly that in nine cases the roentgen-ray diagnosis was unresolved pneumonia in one, tuberculosis in one, abscess in one, and malignancy in six. In our series the diagnosis was repeatedly made clinically while roentgenologists insisted either that the chest was negative, or that the lesion discovered on the plate was tuberculous. Figures 6 to 10 show such cases. A small tumor the size of a cherry, when growing in the center of the pulmonic field, may be seen clearly in the roentgenogram. We see such tumors frequently in secondary growths (fig 1). But primary tumors, as a rule, grow within or near a large bronchus at the root of the lung. The result is that the shadows produced by them merge with those of the other normal and pathologic hilum structures. Infiltrating tumors produce atelectasis in the parenchyma owing to bronchial stenosis. The density seen on the plate may simulate any other subacute or chronic lesion of the lung. In our experience, several cases of metastatic tumors of the lung were revealed by physical signs long before they could be discerned on the roentgenogram. When the tumor reaches larger dimensions it is only rarely shown on the film as a homogeneous, sharply delimited shadow, such as is pathognomonic of mediastinal growths, particularly lymphosarcoma. The lung tumor, growing from a bronchus and infiltrating the lung along the perivascular and peribronchial lymphatics, spreads out from the hilum, producing a shadow not unlike that seen in certain forms of tuberculosis or pneumoconiosis. In many cases, owing to atelectasis

17 Barjon. Etude clinique et radiologique du cancer mediastino-pleuro-pulmonaire, *J de radiol et d'electrol* 5 241 (June) 1921.

18 Bryan, Lloyd. Roentgenological Study of Primary Lung Carcinoma, *J Radiol* 2:1 (Nov) 1921.

resulting from obturation of a large bronchus, the lung tissue beyond the actual tumor appears cloudy on the roentgenogram (figs 3, 4 and 11). In others, in which the neoplasm spreads along the lymphatics, we may see small nodules, like beads, ahead of the main mass, at times following the path of the bronchi, lymphangitis carcinomatosa (fig 5). On the other hand, we have had several cases in which the entire upper lobe was obscured by the tumor producing a homogeneous shadow, with a sharp line of demarcation suggestive of interlobar effusion (figs 14 and 23).

It has been said, though it is not as frequently true as some roentgenologists would lead us to believe, that in tuberculosis a good roentgenogram often shows more extensive changes in the lungs than physical signs would indicate. I would add parenthetically that it depends considerably on who makes the physical examination. The reverse is true of most cases of pulmonary neoplasm. Here, because of plugging or compression of a primary bronchus, physical examination often shows an entire lobe flat on percussion and either feeble or entire absence of breath sounds, this leads to the conclusion that the tumor mass has replaced a large area of the parenchyma or a complete lobe. But the roentgenogram may show only a small or moderate sized tumor at the hilum, while the rest of the lung field is either cloudy, because of atelectasis, or entirely normal.

In rare instances the tumor mass, originating at the hilum, extends across the thorax, while above and below this mass the lung field appears normal. Here we have the suspended shadow that may be seen on the fluoroscopic screen moving with respiration. This picture is not unlike that seen in certain cases of interlobar effusion. Two of the latter sort of cases, diagnosed as tumor, surprised us a few months later when we found that the "neoplasm" had disappeared. The fluid was absorbed (figs 11 and 12). Homogeneous shadows across the chest while the rest of the pulmonary field appears normal may prove baffling to both clinician and roentgenologist. They may indicate tumor or mediastinal or interlobar effusions. In some cases only careful observation for a long period of time will lead to a decisive opinion.

In some cases we have induced a diagnostic pneumothorax for the purpose of clearing up obscure cases.¹⁹ A roentgenogram taken after air is allowed to flow into the pleural cavity collapsing the lung shows the tumor clearly defined (figs 25 and 26). But this can only be done when there are no adhesions preventing the entry of air into the pleura, and pleural adhesions are rather common.

¹⁹ Fishberg, Maurice. Discernment of Intrathoracic Neoplasms by Aid of Diagnostic Pneumothorax, *J A M A* 76:581 (Feb 26) 1921.



Fig 19



Fig 20

Fig 19—Primary carcinoma of left lung with gangrene making a large abscess cavity

Fig 20—Similar carcinoma to one shown in figure 19



Fig 21



Fig 22

Fig 21—Same patient as in figure 20, who had been given a large dose of opiate in the evening, during the night the secretions in the abscess cavity accumulated, filling it

Fig 22—Primary carcinoma of right lung, showing abscess replacing tumor, secretions withdrawn through an exploratory needle showed neoplastic cells, injection of methylene blue colored the sputum immediately

THE PLEURAL FORM

A clinical fact, not sufficiently appreciated, is that more than 50 per cent of tumors of the lung are complicated by pleural effusions. Tumors of the lower lobes are more likely to be thus complicated than those of the upper lobes. In thirty-one of our sixty cases, effusions were observed. In sixteen the effusions were serous, in nine sanguineous, and in six purulent. Tumors of the lower lobe come on more insidiously, hence, some patients present themselves for the first time with the pleura filled with fluid. Error in diagnosis is more common than in neoplasm without pleural effusion. The fluid in the pleura is considered sufficient to account for the symptoms and a diagnosis of pleurisy or empyema is made, coupled with a favorable prognosis.

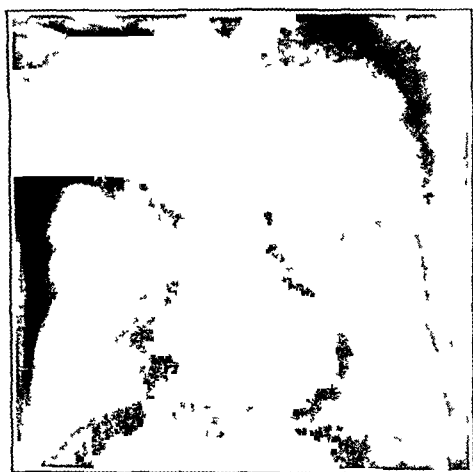


Fig 23



Fig 24

Fig 23—Similar carcinoma to one shown in figure 22, Nov 6, 1923

Fig 24—Same patient as in figure 23, Dec 20, 1923, rapid extension of the tumor, now involving the greater part of the right lung, should be noted

We have found that there are certain clinical features of cancerous effusions which render the diagnosis often quite certain. In three cases operated on for "empyema," surgeons insisted that cancer could be excluded, but necropsies confirmed our conviction that neoplasm of the lung was the primary process.

The age incidence is of importance. Pleurisy complicating tumors of the bronchi and lung occurs mainly in persons over 35 years of age, the vast majority are over 45. Unlike tuberculous and metapneumonic pleurisy the onset is invariably insidious. The patient gives a history of cough, dyspnea, pain in the chest and perhaps hemoptysis for several weeks or months. But these were only slight annoyances and did not urge the patient to seek medical advice. If a physician was consulted tuberculous pleurisy or intercostal neuralgia was diagnosed.

The physical signs of malignant pleurisy are almost pathognomonic. In the vast majority of cases physical exploration of the chest, when the findings are properly interpreted, will differentiate cancerous effusions from those due to other causes.

Tuberculous and metapneumonic effusions are characterized, as is well known, by flatness over the area containing fluid, while immediately above the flat area anteriorly there is a zone of tympany, the so-called skodaic resonance. It is this tympanitic zone that is absent above effusions complicating cancer of the lung. Here, a flat note is elicited not only over the effusion but also much further up the chest wall, in most cases as far up as the clavicle.

It is uncommon that the fluid should fill the entire chest in tuberculous, metapneumonic or rheumatic pleurisy. The causes of the flatness all over the affected hemithorax in cancerous effusions are infiltration of the pulmonary tissue by the neoplasm and atelectasis due to obturation of the supplying bronchus, the flatness due to these causes merging with that of the fluid below. It is noteworthy that displacement of the mediastinum to the opposite side, common in tuberculous and metapneumonic effusions, is exceptional in the cancerous varieties, more commonly the mediastinum is drawn to the affected side, owing to extensive atelectasis.

In pleurisy of tuberculous or metapneumonic origin, breath sounds are audible over the lung above the effusion. In many we hear the changed breath sounds indicating a tuberculous process in the upper lobe of the lung, any variety of râles may be audible, depending on the tuberculous changes in the upper lobe of the lung. These are lacking in cancerous effusions. Furthermore, in advanced tuberculosis complicated by pleural effusion auscultatory signs of a lesion in the opposite lung are almost invariably heard, while in primary cancer the opposite lung remains unaffected for a long time or permanently. Obviously, this point is even better appreciated in a roentgenogram.

Pain in the chest is usually the first symptom complained of by patients affected with pleurisy. With the appearance of the effusion, the pain is either ameliorated or disappears altogether. Dyspnea in a patient with a pleural effusion is not as a rule urgent, orthopnea is uncommon. Tapping will relieve both the pain and the dyspnea in patients with pleural effusions of inflammatory origin. Not so with cancerous pleurisy. The pain remains, and may be severe and lancinating, requiring large doses of morphin for its relief. After tapping dyspnea and orthopnea will remain almost as urgent as they were before a large quantity of fluid was withdrawn from the pleural cavity.

Most roentgenologists agree that the fluid in the pleura covers up the neoplastic growth and that all that can be said when viewing a roentgenogram of such a chest is that there is an effusion. Several

years ago, we¹⁰ introduced the following procedure to clear up this sort of case. The fluid is aspirated as completely as possible and air is then introduced into the pleural cavity, using a pneumothorax apparatus for the purpose. A roentgenogram is then made and the tumor may be seen distinctly (figs 25 to 27). This cannot be done effectively in every case because of pleural adhesions, which are almost as common in cancer of the lung as in tuberculosis.

Cancerous effusions may show rather curious shapes in the roentgenogram. In figure 16 an interlobar effusion is shown as a wedge-shaped, homogeneous shadow, extending horizontally across the chest.



Fig 25



Fig 26

Fig 25—Pleural effusion secondary to primary carcinoma of lung.

Fig 26—Same patient as in figure 25, with diagnostic pneumothorax induced, while complete collapse of the lung could not be obtained because of pleural adhesions, the tumor is seen clearly.

The symptoms and physical signs were those characteristic of neoplasm of the lung. Four months later the tumor had grown to such an extent as to invade three-fourths of the affected hemithorax, and the effusion filled the right pleural cavity.

Exploratory puncture has been carried out in all cases and, unlike our experience with sputum, has often yielded valuable information. It was mentioned above that in the majority of cases the effusion was serous, in sixteen of thirty-one cases the effusion was of this nature. In nine, or 29 per cent, the fluid was sanguineous, while in six, or 19.4 per cent, it was purulent. Attention should be drawn to the high proportion of purulent effusions in cancer of the lung, because we have not met with the statement that empyema is a frequent concomitant of cancer of the lung, though many individual case reports show that pus was found during life or at the necropsy. In one case (fig 15), a serous

effusion was found at the first exploratory puncture, while at subsequent punctures a little distance away from that point, thick, viscid pus was brought out. It was evident that the effusion was multilocular, some pouches containing serum, others pus, and still others serosanguineous fluid. We have met with three such cases.

A careful search has been made to find cancer cells in fluids removed by thoracocentesis. In all cases the examination was carried out by Dr. David P. Secof,²⁰ who has had much experience along these lines. The specimen was centrifugated, the sediment fixed in Orth's solution, embedded, cut, and stained with hematoxylin and eosin. Following this technic, Secof reported the presence of cancer cells in about 70 per cent



Fig 27



Fig 28

Fig 27—Carcinoma of right lung secondary to cancer of stomach, pleural effusion.

Fig 28—Same patient as in figure 27, showing fluid withdrawn from pleura and air let in, tumor is clearly seen.

of fluids from our patients with neoplasm. But it must be mentioned that occasionally even a trained pathologist reports the finding of cancer cells in cases later proved not to be neoplastic. Several such mistakes have occurred in our institution and they constitute a grave limitation of the method. Nevertheless, the microscopic examination of pleural effusions is often a valuable aid in the diagnosis of carcinoma of the lung, and may be the only finding pointing to the existence of such a condition.

The study of the bacterial flora of purulent effusions, while interesting in the individual case, has not yet given us any diagnostic criteria. Various types of pathogenic micro-organisms have been found in the pus taken from patients with cancerous pleurisy.

²⁰ Secof, D. P. The Value of Examining Body Fluids for Tumor Cells, *Proc. New York Path. Soc.* **24**, 1924.

EXCAVATING FORM

A considerable proportion of cases present symptoms not unlike those characteristic of abscess or gangrene of the lung, among the sixty cases in this series, eleven were of this class

The onset was insidious in eight cases, acute in three. The patient coughs mildly for several weeks and expectorates small amounts of sputum, which may be streaky. Later on he may be more or less dyspneic. Sooner or later the sputum becomes more abundant and assumes a fetid odor. The malodorous character of the sputum may be of various degrees. The pungent stench of pulmonary gangrene in its worst aspects is encountered, while in others it is merely disagreeable, suggestive of chronic pulmonary abscess. Hemoptysis is common and may be only slight, but more commonly the bleeding is copious and threatening. I have seen four cases of fatal hemorrhage due to this cause. The fever is slight in some, but in others it is high, running up to 104 F and being continuous, while later on it becomes intermittent, at times suggestive of sepsis or progressive pulmonary tuberculosis. Profuse sweating is not uncommon and some complain of exhausting night sweats. As was already mentioned, some of the patients give a history of an acute onset with high fever, pain in the chest and hemoptysis, and a diagnosis of pneumonia is made. The "pneumonia," however, fails to terminate by crisis and because of the continuation of the fever, cough and fetid sputum, a diagnosis of metapneumonic abscess or empyema is made.

The diagnosis of this class of cases is obviously difficult, presenting as they do clear cut stigmas of well known diseases. In pulmonary abscess we often find a known etiologic factor—tonsillectomy, some surgical operation on the upper respiratory tract or mouth, extraction of teeth, aspiration of a foreign body or submersion. The symptoms, fever, cough, pain and expectoration of fetid sputum, make their appearance in from seven to fourteen days after the surgical insult. In metapneumonic abscesses we have a history of pneumonia, which began with a chill, fever, cough and rusty sputum. In cancerous disease of this type, the cough and expectoration have, as a rule, been annoying several weeks or months, when suddenly fever makes its appearance and the sputum becomes fetid. In fact, in our inquiries in cases that began with so-called pneumonia, with but one exception, we elicited the information that the cough, dyspnea, pain and hemoptysis preceded the fever and fetid sputum by several weeks.

The physical signs also point to greater condensation of lung tissue than is found in nonmalignant lung abscesses. Pulmonary abscess cannot as a rule be localized by a physical exploration of the chest. Moreover, flatness over the lesion is exceptional. Over large abscesses tympany is more often elicited on percussion. In abscesses due to

neoplasm, the entire upper lobe is flat, as was already described when discussing the first group of cases. In growths of the lower lobe, the flatness is elicited, as a rule, over only one aspect of the chest, the anterior or the posterior, while the resonance over the other aspect is either normal or but slightly impaired. This is a point that will bear emphasis. If we find flatness anteriorly while posteriorly the resonance is normal, or the reverse, a tumor is to be suspected. Adventitious sounds, such as large and medium sized moist or bubbling râles, when found, are usually of the same character in cancerous abscess as in abscesses of other origin. But in most cases none are perceived. The diagnosis of these cases thus rests merely on the history of an insidious onset and flatness on percussion, coupled with the age period at which cancer usually occurs. Now and then microscopic examination of the sputum will reveal cancer cells. But we have already indicated that absolute reliance cannot be placed on either positive or negative cytologic findings.

The roentgen-ray findings in these cases are also not uniformly diagnostic. In some cases the picture is that of pulmonary tuberculosis or abscess. Figures 21 to 23 show roentgenograms of a case in which we diagnosed abscess clinically. Examination of the pus drawn with an aspirating needle showed neoplastic cells. Injection of a solution of methylene blue colored the sputum immediately. However, the diagnosis must be made clinically, roentgenologically too many failures will be reported.

There is one form of cancerous abscess of the lung which can be diagnosed only with the aid of the roentgen rays. It occurs in the center of a lobe, presumably being derived from the epithelium of the smaller bronchi or alveoli and not from the more common origin of the larger bronchi or bronchial mucous glands. It appears that the neoplasm breaks down quickly in these cases, either as a result of lack of nutrition owing to outgrowing the blood supply or because of secondary infection. At any event, the broken down neoplastic tissue is expectorated, leaving a larger or smaller cavity surrounded by a thin wall. As will be seen from the roentgenograms (figs 21 to 22), the cavity may be completely or partly filled with secretions. Giving the patient a large dose of an opiate in the evening will result in his retaining the secretions in the cavity and the next morning the roentgenogram will show the cavity filled. In two cases of somewhat similar cavities the upper lobe of the lung was completely excavated and filled with secretions. It will be noted that the lower margin of the abscess corresponds to the interlobar fissure which prevents for a time the extension of the tumor. However, later on the growth invades the lower lobe (figs 23 and 24).

This type of neoplastic disease of the lung can best be diagnosed with the aid of the roentgen rays. However, an echinococcus cyst gives a

similar roentgenogram and the symptomatology may not be unlike that of cancerous abscess. Finding of the scolices, hooklets or cyst membrane in the sputum, eosinophilia, and perhaps a hydatid cyst in the liver or elsewhere, as well as the complement fixation test for echinococcus disease will differentiate it from cancer.

DURATION OF LIFE

Primary cancer of the lung is not as rapidly fatal as carcinoma of most other organs. While we have seen some cases that terminated fatally in less than six months after the appearance of the first symptoms, the majority lasted more than one year. One patient lasted four years and I have seen a patient with sarcoma of the lung who lived for five years after the onset of the disease. It is noteworthy that there may be remissions in the progress of the disease during which the patient feels comparatively well for weeks or months. In several cases the growth remained stationary in size and no metastases occurred, the patients feeling well and even gaining in weight and strength considerably, and we began to suspect the reliability of the diagnosis. But later on the neoplasm broke down, sent out metastases and the course was rapidly downward. This point is to be borne in mind when rendering clinical judgment in cases of neoplastic disease of the lung.

THE DIAGNOSTIC AID IN EVALUATING THE VIGOR OF INSPIRATORY COSTAL EXCURSION *

C F HOOVER, M D

CLLVELAND

The vigor with which the arches of the ribs move in an inspiratory direction is determined by the excess of inspiratory force of costal movement over the counterbalancing or restraining agencies that retard the movement of the ribs

In inspiration the thorax is enlarged circumferentially and longitudinally by the scaleni and the intercostal muscles and the diaphragm. The muscles that increase the circumference of the thorax (the scaleni and intercostals) and the diaphragm, which increases its length, must mutually counterbalance and overcome each other. To appreciate this fundamental and important fact, one should study a patient in whom paresis of all these muscles is sufficient to preclude their action in concert but which still affords sufficient power to enable them to function separately

Such a patient recently entered the women's ward at Lakeside Hospital. She was 40 years old and had a chronic poliomyelitis anterior that involved all the neck muscles, the intercostals, and both forearms, thighs and legs. All the neurologic symptoms were motor and trophic. There were no symptoms of sensory impairment. As the patient lay in bed, quietly breathing twenty times a minute, the entire thoracic cage moved in an expiratory direction during inspiration as the abdomen was protruded by phrenic excursion. The manubrium and all the ribs moved caudad in inspiration, and the costal margins moved mediad. When the patient was watched for a time, it was observed that occasionally (about every tenth inspiration) she enlarged her thorax circumferentially but never on these occasions was there any evidence of phrenic excursion. It was apparent that in automatic respiration the muscles that enlarged the circumference of the thorax and the diaphragm, which enlarged its length, had sufficient power to function singly but not in unison. When instructed to take a deep breath, the patient either lifted and enlarged the circumference of the thorax without increasing the length or she increased its length by abdominal breathing without increasing its circumference. In other words there was sufficient strength in the scaleni and intercostal muscles to overcome the retractility of the lungs when unopposed by the diaphragm

* From the department of medicine of Western Reserve University at Lakeside Hospital

* Read at the meeting of the Association of American Physicians, Washington, D C, May, 1925

and the lungs could be extended by the diaphragm when unopposed by the scaleni and intercostal muscles. Her expected vital capacity when she was lying down was 3,700 cc., but she could never show a vital capacity above 1,400 cc. This patient shows in a striking way how the inspiratory function is impaired when there is sufficient muscular vigor to overcome the retractility of the lungs but not enough to maintain the normal reciprocal counterbalancing between the scalenocostal and the phrenic forces. In this case the want of costal force of excursion was clearly shown to inspection as well as to palpation. In many other cases, however, we have to deal with other counterbalancing factors that reduce the vigor of costal excursion in one entire side or a part of one side, when the visible delay or diminution of excursion is imperceptible but the lessened force of costal excursion as perceived by the palpating fingers is pronounced.

Every experienced examiner must often have perceived how much more distinctly he could palpate than see a disparity in excursion in symmetrical chest regions. This disparity is not due to a more delicate perception by the hand of differences in time or distance of excursion but to the perception of the comparative force of excursion. If one directs his attention to the comparative force of excursion, evidence will be got for disturbances in pulmonary ventilation that quite escape inspection.

STENOSIS OF A BRONCHUS

There may be considerable stenosis of the main bronchus to a lung that will yield no other physical sign than diminished force of costal excursion on the affected side. Percussion resonance may be unchanged. Auscultation may reveal no diminution in the intensity of the transmitted respiratory or vocal sounds, and even the palpable vocal fremitus may not be lessened, although the coarse palpable vibrations may be diminished by a moderate degree of bronchial stenosis that will not impede the transmission of audible sounds.

Inspection may not reveal a disparity in excursion, but the palpable lessened force of excursion is clearly perceived.

REPORT OF CASE

A patient who had an aneurysm of the transverse aortic arch showed no signs to percussion, inspection or auscultation. However, when the ear was applied over the region of the transverse arch, a deep systolic impulse and a diastolic impact were detected. There was no visible disparity in the extent of excursion of the two sides, but when a vigorous inspiratory effort was made, the lessened vigor of excursion on the left side was pronounced. An attempt to restrain the upper right ribs in their movement in a cephalic direction was ineffectual, but when the examining fingers were hooked over the upper borders of the ribs in the midclavicular and axillary lines of the left side, the costal excursion could be restrained and the force of their excursion was lessened to a marked degree.

The use of the fluoroscope confirmed the diagnosis, but the impaired vigor of costal excursion was the weightiest physical sign brought out by objective examination

The same sign was often observed in other thoracic diseases, but there was no way in which the disparity in the vigor of costal excursion could be recorded or evaluated. In unilateral bronchial stenosis, however, it seemed possible to arrive at a mathematical comparative evaluation of the effects on the time and on the vigor of excursion of the affected side. It is obvious that if one bronchus has its lumen reduced one-half and the distensibilities of the lungs are equal, then, assuming the activation strength of the inspiratory muscles on the two sides to be equal, the side with the narrowed bronchus must move with a diminution of vigor that is determined by the degree of stenosis. So will the affected side attain a lesser expansion, which can be expressed by the prolongation of time that would be required to attain a normal distention of the lung with the stenosed bronchus. The lessened vigor of excursion can be expressed mathematically by determining how much more the barometric pressure must be lowered on the side of the narrowed bronchus to counterbalance the resistance of the bronchial stenosis, or, in other words, how much greater suction must be employed on the side of the narrowed bronchus to give the same vigor of excursion as exists on the opposite normal side. This difference in vigor of excursion is perceptible only to palpation. The delay in time of excursion is perceived by inspection.

The following problem was presented to a consulting engineer, Victor Phillips, who kindly gave me the method of its solution employed in engineering when the transmission of air pressure is used

Problem—If a normal man is able to inhale 4,000 cc of air in one second and then the bronchus of one side has its lumen narrowed from 0.8 cm^2 to 0.4 cm^2 , how much will the pleural suction on the affected side have to be increased to provide it with a volume flow per second of 2,000 cc of air? Also, how much will the time of inspiration have to be prolonged to procure a flow of 2,000 cc through the narrowed bronchus if the pleural suction remains the same on both sides?

The answer to the first problem gives us a mathematical expression of the palpable loss of vigor of costal excursion on the side with the bronchial stenosis, and the answer to the second gives a mathematical interpretation to the visible delay in costal excursion. The solutions of the two problems show that the suction would have to be increased 185 per cent, whereas the time factor would have to be increased only 67 per cent. These results strikingly contrast the palpable with the visible evidences for restraint to pulmonary excursion from bronchial stenosis. In other words, we palpate the 185 per cent and see the 67 per cent.

The pressure drop (or gradient) necessary to force a gas through an orifice or tube varies with the square of the velocity of the gas. It follows, therefore, that even a small restriction in one of the bronchi alters materially the normal pressure relations governing the flow of air into and out of the lungs. How great may be the unbalancing effect between the two lungs by a restriction in one of

the bronchi may be strikingly illustrated by the well known laws of physics for the flow of gases. The general relationship may be expressed
$$h = \frac{K}{C} \times 2 \times \frac{V^2}{2g}$$
 in which

h = the pressure drop through that part of the bronchus under consideration (millimeters of mercury)

V = air velocity at the same point (feet per second)

C = a constant expressing the resistance or friction of the same part of the bronchus

K = a constant calculated from the temperature of the air and the atmospheric pressure

g = the accelerative force of gravity (feet per second)

Let it be assumed that the normal of the two bronchi has a sectional area of 0.8 cm² and the restricted bronchus an area of 0.4 cm². Assume further a normal inhalation of 2,000 cc of air in one second to each lung (72 F and 29.92 pounds atmospheric pressure). The effect of the restriction of area from 0.8 to 0.4 cm² may then be calculated rather precisely. Limiting consideration to a short length of the bronchus, say 1 inch (2.5 cm), within which length the restriction in question will be entirely contained, then for the conditions assumed in the foregoing the normal pressure drop through the 1 inch of bronchus will be 3.5 mm of mercury. If the other lung is to inhale this *same volume* of air in the *same space of time*, then the pressure drop through the corresponding 1 inch of bronchus in which the restriction exists will be 31.2 mm of mercury. Since for this condition (of equal volumes in the same time to both lungs) the pressure drops through the other parts of the trachea, bronchi and bronchial tubes will not be affected by the restriction, it follows that 31.2—3.5 = 27.7 mm of mercury is the increased drop or suction that must be produced by the muscular action of the chest walls in order to make both lungs function alike. Suppose, now, that the normal pressure difference between atmosphere and the pleural cavity is 15 mm of mercury, then it is apparent that the foregoing "drag" on the chest walls would be increased on the restricted side to a total of 42.7, or nearly three times the "drag" on the normal. The exact amount of this increase in drag in any particular instance will, of course, vary materially not only with the amount of the restriction, but also with the shape and character of the restriction which will determine the friction constant (C) referred to above. The constants used in the foregoing calculations are those used in engineering for restricted tubes sufficiently similar to the bronchi to render the results comparatively accurate.

As a matter of fact, the same volume of air would not be inhaled through the restricted bronchus as through the normal bronchus *in the same length of time*. Some further idea may therefore be had as to the effect of restriction by calculating the additional time necessary to inhale the same volume of air if the pleural cavity suction is the same for both lungs. In the first example the time for inhaling 2,000 cc into each lung was 1 second and to accomplish this required nearly three times the suction on the restricted side, or more precisely an increase of 185 per cent over that on the normal side. With the *same suction* on both sides, the other conditions remaining unchanged, there would be required 1.67 seconds to inhale the same volume through the restricted bronchus as against 1 second for the normal bronchus, an increase of 67 per cent. In other words, the condition of restriction in one bronchus is more strikingly apparent in what may be termed the drag against which the chest walls must act than it is expressed in terms of time delay. That this is true may be briefly restated as follows. Pressure drop increases with the square of the velocity, whereas time of inhalation varies inversely with the first power of the velocity.

When thus mathematically expressed, we see why the vigor of excursion is such a delicate measure of the drag or counterbalance on the inspiratory excursion of a lung. There is no method by which this

disparity in vigor of excursion can be quantitatively estimated. It can be clearly evaluated by manual examination, but no instrument of precision can be employed.

In several former articles I have interpreted and explained the significance of asymmetry in the excursion of the costal borders. Further observations on this subject lead to the conviction that the comparative vigor of excursion of the costal borders is a more delicate test than the comparative extent of excursion. The delicacy of this test is shown by the fact that in normal subjects the subcostal angle widens symmetrically with inspiration, but the left costal margin moves normally with less vigor than the right. The reason for this is the fact that the subcardial diaphragm to the left of the median line is slightly less convex than to the right. The difference in convexity under normal conditions is not sufficient to cause asymmetry in extent of excursion of the two inner halves of the costal margins, but the less vigorous excursion on the left is clearly perceived if the two borders are alternately restrained during forced inspiration. It will be perceived that the left moves with less vigor under the restraining hand than the right. By comparing the vigor of lateral movement of the inner and outer halves of a costal margin or symmetrical parts of opposite sides we can obtain a clear perception of the comparative drag on the lateral movement of the costal ends that originates from disparity in convexity of the diaphragm of the two sides.

PARESIS OF THE INTERCOSTAL MUSCLES OF ONE SIDE

In hemiparesis of cerebral origin or in regional disease of the spinal cord, the vigor of costal excursion is lessened as well as the vigor of movement of other skeletal muscles. It is not detected when only the extent of costal movement is observed and the vigor of movement is neglected. The intercostals have a bihemispherical supply quite like the frontalis.

The familiar method of differentiating a supranuclear from a nuclear or infranuclear facial palsy is to determine the shape of the frontalis in the paresis. We find, however, that, although the forehead may be symmetrically wrinkled in cases of cerebral facial paresis, the wrinkles are not so firmly held against a smoothing pressure on the affected side. It is exactly the same with the intercostal muscles.

In some cases of cerebral palsy the thorax of the affected side can be seen to have a diminished extent of excursion, in other cases the two sides are seen to move symmetrically. But in all cases of complete cerebral hemiparesis or when the upper and lower extremities of one side are involved, the vigor of costal excursion is diminished on the affected side. The neurologists have differed in their opinions on this subject because they have observed only the extent of costal movement.

It is true that in many cases the extent of excursion is symmetrical on the two sides, but if the patient makes forced inspirations and the vigor of costal movement on the two sides is alternately compared, the ribs on the paretic side will always be found to move with less vigor. There may be sufficient strength on the affected side to compress and expand the lung to its maximum capacity or so nearly to it that an examiner will be in doubt about lessening of the vital capacity. The limit of pulmonary expansion is not determined by the strength of the respiratory muscles but by the maximum extensibility of the visceral pleura and pulmonary parenchyma. There may be quite enough strength in the paretic intercostal muscles to contribute their adequate share to expansion and compression of the lungs, but when compared with the normal side the ribs on the paretic side will always be found to move with less vigor against resistance.

In cases of cord syphilis and syringomyelia, the paresis of intercostal muscles may not be sufficient to lessen the extent of costal excursion, but when the upper ribs are suspected of involvement the vigor of excursion should be tested by hooking the fingers over the upper borders of the ribs in an effort to restrain their cephalad movement in a forced inspiration. Paresis of the lower five intercostal muscles should be tested by palpating the vigor with which the outer half of the costal margin moves laterad in a forced inspiration.

In cases of transverse myelitis or cord tumor, the vigor of movement of the ribs aids in localizing the upper limits of the lesion. I recently saw a patient who had a complete sensory and motor paraplegia inferior. The upper limit of the anesthesia was in the sixth intercostal space. When the patient made a series of forced inspirations it was found that the sixth ribs moved with a vigor that could not be restrained, whereas the seventh ribs could easily be restrained in their cephalad movement. A moderate amount of practice enables one to recognize which ribs are moved by paretic intercostal muscles.

The disparity between the visible and palpable evidences for counterbalancing of the force of inspiratory thoracic excursion is just as pronounced when resistance to lung extension lies in diminished extensibility from disease of the lung or visceral pleura. Nearly all the physical signs we employ in studying the lung are directed toward detection of changes in its size, density and extensibility, but extensibility is the first physical attribute to be affected in any disease of the bronchi, parenchyma or visceral pleura, and the most sensitive test that can be employed to detect the counterbalancing of lung resistance to the force of extension is to study the comparative vigor of costal excursion over symmetrical regions.

Incipient tuberculosis of the lung will affect the vigor of costal excursion over the site of its location when inspection, percussion, pal-

pation and the roentgen ray fail to give any evidences. It is therefore of great assistance in the early diagnosis of tuberculosis of the upper lobes of the lung to compare the vigor of costal excursion on the two sides over the second, third and fourth ribs. This should, of course, always be done when the patient is recumbent, so that there may be no restraint to costal excursion from the abdominal muscles.

I have frequently been able to detect a lessened vigor of excursion in the upper ribs in patients who had no other symptom than hemoptysis when all other methods of examination failed to indicate which was the affected side.

In former years the functions of the scaleni and intercostal muscles and the diaphragm were so misconceived that an analytic examination of thoracic excursion was impossible. To make a critical examination of respiratory excursion is obligatory on the internist, neurologist and surgeon, because it yields valuable information in the study of medical and surgical diseases of the thorax and upper part of the abdomen, and also in diseases of the brain and spinal cord. When we study the counterbalancing between the force of costal excursion and extensibility of the lung, we gain information about a physical attribute of the lung, which is most sensitive to all its pathologic lesions, and reciprocally we also have a sensitive method for detecting impairment in the nerve supply to inspiratory muscles.

SUMMARY

When the action of the inspiratory muscles is (in a pulmonary region) opposed by some other factor than the normal retractility of the lung, or when there is a regional paresis of intercostal muscles, the vigor with which the ribs concerned move in an inspiratory direction offers a more delicate method for detecting the counterbalancing of the costal excursion than does inspection of the extent of excursion. The added drag that is perceived by palpation can be expressed by a mathematical formula when stenosis of one large bronchus is concerned. The lessened vigor of excursion of the ribs in any region will give evidence for any lesion that may diminish the extensibility of the underlying lung when the extent of excursion may reveal no evidence and when percussion and auscultation reveal no evidence for diminished resonance or increased density of the lung and when adventitious auscultatory signs are wanting. Diminished vigor of excursion of ribs should be studied in a routine manner because the vigor of costal excursion over any pulmonary region accurately mirrors the extensibility of the underlying lung. Because extensibility is the first attribute affected in all pulmonary diseases, any impairment of this attribute offers the earliest procurable evidence for regional lung disease.

CORRIGAN'S DESCRIPTION OF AORTIC INSUFFICIENCY

EDITED, WITH A NOTE

LOGAN CLENDENING

KANSAS CITY, MO

[NOTE—Sir Dominic John Corrigan, the author of the marvelous record of clinical observation reprinted below, was according to the *Lancet's* notice at the time of his death "a perfect Irishman." He practiced medicine during most of his life in Dublin, a dominant member of that brilliant group of physicians who resided there in the early part of the nineteenth century—Graves, Stokes, Robert Adams, William Wallace, who first popularized the use of iodide of potash, and Francis Rynd, the inventor of the hypodermic, being his colleagues, and John Cheyne and Colles of a slightly earlier generation.

It is worth noting that he puts himself down as one of the physicians to the Charitable Infirmary, Jervis Street, Dublin. This hospital had beds for only six patients at a time, and this scanty material was probably the basis for Corrigan's observations which led to the accurate account of the pulse signs and other phenomena of aortic insufficiency.

He was born in 1802, six years after Graves and two years before Stokes. He received his medical education at Sir Patrick Dun's Hospital, afterward matriculating at the University of Edinburgh where he received his doctor of medicine degree in 1825, returning to Dublin to take up active practice.

The paper from which he derives most of his fame was published, as can be noted below, in the *Edinburgh Medical and Surgical Journal* in 1832. His later description of fibroid phthisis, or as he called it "cirrhosis of the lung," attracted perhaps even more attention in his life time. He had an enormous fame in his own day both as a lecturer and as a consultant, and he used to tell, with great uncton, how he had to have a secret doorway built in his house in order to escape from the throngs of patients. After playing an important part in the handling of the Irish famine fever in 1847 and serving some terms in Parliament he died in 1880. The most easily obtainable sketch of his life is probably in Walsh's "Makers of Modern Medicine," Fordham University Press, New York, 1907.

The best introduction to his character and labors is to be found in the appended article "The superb plate," to use the words of Dr. Fielding Garrison, accompanying the original paper is reproduced from a photograph. Two final comments may be made. First, the work of the great Irish school is a fine appendage to Laennec's introduction of the stethoscope. Laennec's interest was centered on the lungs, the portions of his book dealing with the heart are plainly inferior. But the extension of the use of the stethoscope to heart disease was worked out, to no minor extent, by the Dublin group. Second, this paper is reprinted because the medical journal in which it appeared is far from easy of access to most students of medical history in this country. Up to the end of the eighteenth century when a man had a medical observation to make he usually published it in a book. These books, such as Jenner's "Inquiry" and Withering's "Account of the Foxglove" turn up at booksellers every once in a while and are fairly well distributed in libraries, private or public. But with the beginning of the practice of publication in circulating magazines, the great original clinical descriptions of diseases are more and more likely to be out of the student's reach and for that reason should be reprinted from time to time.

Aortic valve disease had been described before Corrigan by Cowper, Vieussens and Hodgkin, but he gave the first account of the arterial signs.]

ON PERMANENT PATENCY OF THE MOUTH OF THE
AORTA OR INADEQUACY OF THE AORTIC VALVES

D J CORRIGAN, M D One of the physicians to the Charitable Infirmary, Jervis Street, Dublin, lecturer on the theory and practice of medicine, consulting physician to St Patrick's College, Maynooth, Ireland

(*From the Edinburgh Medical and Surgical Journal*, April 1, 1832)

The disease to which the above name is given has not, so far as I am aware, been described in any of the works on diseases of the heart. The object of the present paper is to supply that deficiency. The disease is not uncommon. It forms a considerable proportion of cases of deranged action of the heart, and it deserves attention from its peculiar signs, its progress, and its treatment. The pathologic essence of the disease consists in inefficiency of the valvular apparatus at the mouth of the aorta, in consequence of which the blood sent into the aorta regurgitates into the ventricle. This regurgitation, and the sign by which it is denoted, are not necessarily connected with one particular change of structure in the valvular apparatus, and hence the name, "Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves," has been chosen as simply expressing such a state of the parts as permits the regurgitation to occur.

I have been in the habit for some years of describing this disease under the name of inadequacy of the aortic valves, but Dr Elliotson, in his elegantly written work on diseases of the heart, has given to a somewhat analogous morbid state of the auriculoventricular opening a better name, permanent patency. I have, for this reason and for the sake of uniformity, adopted the term, and I shall continue to use it as synonymous with my own term, inadequacy of the aortic valves.

The morbid affections of the valves and aorta permitting this regurgitation are the following

First, the valves may be absorbed in patches, and thus become reticulated and present holes, through which the blood flows back into the ventricle.

Second, one or more of the valves may be ruptured, the ruptured valves, when pressed, flopping back into the ventricle instead of catching and supporting the column of blood in the aorta, the blood then regurgitating through the space left by the broken valves.

Third, the valves may be tightened or curled in against the sides of the aorta, so that they cannot spread across its mouth, and an opening is then left between the valves, in the center of the vessel, through which the blood flows freely back into the ventricle.

Fourth, the valves without any proper organic lesion may be rendered inadequate to their function by dilatation of the mouth of the aorta. The aorta, affected by aneurysm, or dilated, as it frequently is in elderly persons about its arch will sometimes have the dilatation extend-

ing to the mouth of the vessel, and in such a case, the valves become inadequate to their function, not from any disease in themselves, but from the mouth of the aorta dilating to such a diameter as to render the valves unable to meet in the center the blood then, as in the other instances, regurgitates freely into the ventricle

GENERAL SYMPTOMS

On the general symptoms that accompany this disease, little is necessary to be said. Like most of those connected with affections of the respiratory and circulating organs, they are uncertain and unsatisfactory. There are frequently convulsive fits of coughing, more or less dyspnea, a sense of straitness and oppression across the chest, palpitations after exercise, sounds of rushing in the ears, and inability to lie down. Neither one nor all of these symptoms are essential to the disease. They may all arise from varied affections of the lungs, heart, liver or nervous system. They neither tell us the seat of the disease nor the extent of the danger.

SIGNS

What is deficient in general symptoms from their obscurity is, however, amply supplied by the certainty of the physical and stethoscopic signs, which may be referred to the three following indications: (1) visible pulsation of the arteries of the head and superior extremities, (2) bruit de soufflet and frémissement, or a peculiar rushing thrill felt by the finger, in the carotids and subclavians. In conjunction with these may be reckoned the pulse, which is invariably full. When a patient affected by the disease is stripped, the arterial trunks of the head, neck and superior extremities immediately catch the eye by their singular pulsation. At each diastole the subclavian, carotid, temporal, brachial, and in some cases even the palmar arteries, are suddenly thrown from their bed, bounding up under the skin. The pulsation of these arteries may be observed in a healthy person through a considerable portion of their tract, and become still more marked after exercise or exertion, but in the disease now under consideration, the degree to which the vessels are thrown out is excessive. Though a moment before unmarked they are at each pulsation thrown out on the surface in the strongest relief. From its singular and striking appearance, the name of visible pulsation is given to this beating of the arteries. It is accompanied with bruit de soufflet in the ascending aorta, carotids and subclavians, and in the carotids and subclavians where they can be examined by the finger, there is felt frémissement, or the peculiar rushing thrill, accompanying with bruit de soufflet each diastole of these vessels. These three signs are so intimately connected with the pathological causes of the disease, and arise so directly from the mechanical inadequacy of the valves, that they

afford unerring indications of the nature of the disease. In order to understand their value, it is necessary to consider their connection with the cause by which they are produced. The visible pulsation of the arteries of the neck, etc., may be first examined.

In the perfect state of the mechanism at the mouth of the aorta, the semilunar valves, immediately after each contraction of the ventricle, are thrown back across the mouth of the aorta by the pressure of the blood beyond them, and when adequate to their function of closing the mouth of this vessel, they retain in the aorta the blood sent in from the ventricle, thus keeping the aorta and larger vessels distended. These vessels consequently preserve nearly the same bulk during their systole and diastole. But when the semilunar valves, from any of the causes enumerated, become incapable of closing the mouth of the aorta, then after each contraction of the ventricle, a portion of the blood just sent into the aorta, greater or less, according to the degree of the inadequacy of the valves, returns back into the ventricle. Hence the ascending aorta and arteries arising from it, pouring back a portion of their contained blood, become, after each contraction of the ventricle, flaccid or lessened in their diameter. While they are in this state, the ventricle again contracts and again impels quickly into these vessels a quantity of blood which suddenly and greatly dilates them. The diastole of these vessels is marked by so sudden and so great an increase of size as to present the visible pulsation which constitutes one of the signs of the disease.

That this visible pulsation of the arteries is owing to the mechanical cause here assigned is made evident by several circumstances. It is most distinct in the arteries of the head and neck, which empty themselves most easily into the aorta, and of course into the ventricle. In the arteries of the lower extremities, of even larger size than those which present it above the head and neck, it is not seen to any comparative degree, and most generally not at all while the patient is standing or sitting. It is much more marked in arteries of the head and neck in the erect than in the horizontal posture, and a patient suffering under the disease himself first pointed out a circumstance which is convincing of its being produced as asserted. He could increase the pulsation of the brachial and palmar arteries in a most striking degree by merely elevating his arms to a perpendicular position above his head. He thus enabled the brachial and palmar arteries to empty themselves more easily back upon the aorta. They became more flaccid, and then, on the next contraction of the ventricle, their diastole became comparatively greater, and their visible pulsation of course, more marked. The same effect could be produced in the arteries of the lower extremities by lying down and elevating the legs on an inclined plane. The strength of the heart has little to do in producing this singular pulsation for it is

never observed in an equal degree, and most generally not at all, in the arteries of the lower extremities

If it be asked, is the explanation here adduced of the cause of this visible pulsation sufficient to account for its appearance in the brachial and radial arteries, since the blood to return back from these vessels into the arch of the aorta should flow upwards when the patient holds his arms in the ordinary position, flexed or hanging by his side, the following reply may be made. When the subclavians are pouring back their blood into the arch of the aorta and ventricle, the elasticity of the brachial arteries acting upon the blood just urged into them, forces it back along with the retrograde current of the subclavians, no obstacle meeting it in that direction. The brachial arteries thus partially empty themselves and become in their systole of a lessened diameter, like the carotids and subclavians, but in less degree. The next jet of blood from the ventricle dilates them, and as in the subclavians, produces in them a visible pulsation, and if they be assisted in returning their blood by elevating the arms to a perpendicular position, their pulsation becomes, as has been already observed, much more strongly marked. The arteries of the lower extremities are not similarly circumstanced. The arteries of the upper extremities are assisted in emptying themselves back towards the heart, by the retrograde current in the subclavians and ascending aorta, but on the blood contained in the arteries of the lower extremities, the tall column of blood in the descending aorta is pressing, and prevents any return, or if it be supposed that of the large mass of blood in the descending aorta, a small portion flows back into the arch, it can produce little change in the contents of the iliacs and femorals, and moreover, whether the column of blood in the aorta be lessened or not in diameter, the pressure on the contained blood of the iliacs and femorals will remain the same, and keep these vessels distended. If we, however, as already observed, alter the relation of the several arteries to the arch of the aorta, so as to facilitate the reflux of their contained blood, for instance, from the radial arteries, by raising the arms to a perpendicular line above the head, from the iliacs and femorals by placing the patient in a recumbent posture and raising the legs upward on an inclined plane, the visible pulsation becomes much more marked in these respective arteries.

The bruit de soufflet, which is heard in the ascending aorta, carotids and subclavians with the accompanying frémissement in the latter arteries is next to be considered. The bruit de soufflet characterizing this disease is heard as already observed, in the ascending aorta, its arch, and in the carotids and subclavians. It can be followed upwards from the fourth rib along the course of the aorta increasing in loudness as it ascends, until it is heard of great intensity in the upper part of the

sternum, where the arch of the aorta most nearly approaches this bone, and then branching to the right and left, it can be traced into the carotids and subclavians of both sides, and in these trunks it assumes a harshness that it did not possess in the aorta. This bruit de soufflet is synchronous with the visible pulsation, with the diastole of the arteries. It is of no consequence whether the ascending aorta and its large branches be sound or be diseased, this bruit de soufflet is as loud in the one case as in the other. To account for the presence of this sign, and why it extends so far from the seat of the disease and along sound vessels it is necessary to refer to a paper published in the *Lancet* of 1829, volume 2, page 1. Continued observations from the date of that paper to the present have confirmed the view then taken of the cause of that singular sound, of its being dependent purely upon a physical cause, on a mechanical change in the manner of the blood's flowing.

In that paper is related an experiment, which may be well to recapitulate here. A flexible tube, such as a piece of small intestine, or a portion of artery is connected by one end with a tube which has a current of water of considerable force running through it. While the piece of intestine or artery is kept fully distended by the supply of water from the tube no sound is produced by the motion of the fluid, but if the flexible tube, while the fluid is moving through it, be pressed upon in any part, so that the quantity of fluid passing through the contracted part is no longer sufficient to keep the further portion of the tube tense, then, beyond the contracted part, where the tube is less tense, or in some degree flaccid, a distinct, and, according to the velocity or force of the current, a loud bruit de soufflet is heard, and, at the same time, if the finger be gently laid on the part of the tube where the bruit de soufflet is heard, a slight trembling of the tube is perceived, evidently arising from the vibrations into which the current within is throwing its sides. If in place of constricting any one part of the flexible tube the whole tract of tube be allowed to become partially flaccid, by diminishing the supply of fluid, and the fluid be then allowed to rush along the tube by jets, at each jet the tube is suddenly distended, resembling the visible pulsation described above, and with each diastole of the tube, there is a sudden and loud bruit de soufflet, and, synchronous with the bruit de soufflet there is frémissement felt by the finger.

Both the sound heard and the sensation felt by the finger in this experiment may be explained by the principles which regulate the motion of fluids. It may be remarked that it is a property of fluid in motion that, when discharging itself from the orifice of a tube into open space, or into a vessel of wider capacity not fully distended, its particles move in lines from the orifice, like so many radii tending to leave vacuums between them. When the flexible tube, artery or intestine, therefore, is kept fully distended, the fluid moves forward as a mass,

there is no tendency in its particles to separate one from another—they all press equally—there is no vibratory motion of the sides of the tube, and consequently no sound, and no frémissement or trembling. But if the tube be not kept fully distended, then the fluid propelled through it rushes along as a current, and its particles tend to leave particles between them, throw the sides of the tubes into vibrations, which can be very distinctly felt by the finger, and which give to the ear the peculiar sound *bruit de soufflet*, and to the touch *frémissement*.

These principles may be applied to the state of the ascending aorta and its branches in the instances before us. When the aortic valves are fully distended to their function of perfectly closing the mouth of the aorta, and preventing any regurgitation of blood, the aorta and its branches are kept fully distended, the blood is at each contraction of the ventricle propelled forward *en masse*, and there is no trembling or vibratory motion of the sides of the aorta, carotids and subclavians, and as in the flexible tube when fully distended, no sound is emitted. But when the valves, having become inadequate to their office, permit some of the blood contained in the ascending aorta, carotids and subclavians to return to the left ventricle after each contraction then the aorta and the trunks become, like the flexible tube in the second part of the experiment partially flaccid, and at the next contraction of the ventricle the blood propelled into them is sent along as a rushing current, which throws the sides of these arteries into vibrations, and these vibrations give to the ear *bruit de soufflet* and to the finger *frémissement*. These two signs may be traced to a varying distance from the mouth of the aorta and always along the carotids, and to the outer third of the subclavians, and sometimes in the brachial arteries, as far as the bend of the arm, the distance to which they are heard being determined by the limit to which the current-like motion of the blood producing them is extended. In those cases in which the deficiency of the valves is considerable, allowing a full stream of blood to rush back into the ventricle, there is heard in the ascending aorta a double bruit, the first accompanying the diastole of the artery, the second immediately succeeding, and in listening to the two sounds, constituting this double *bruit de soufflet* the impression made distinctly on the ear is that the first sound is from a rushing of blood up the aorta, the second from a rushing of it back into the ventricle. It is impossible for those who have not heard this double bruit to conceive the distinctness with which the condition described is made on the ear. A patient in one instance heard the double sound distinctly in his own person, and referred it to its cause a rushing of blood from and to the heart. The *bruit de soufflet* and *frémissement* are not perceived in the arteries of the lower extremities when the patient is in the sitting or standing posture. The pressure of the blood in the abdominal aorta is sufficient in these postures to keep

the vessels arising from it fully distended, and thus no vibratory motion of their parietes being permitted, there is no bellows sound, nor *fremissement* or rushing thrill

HISTORY AND PROGRESS OF THE DISEASE

Of eleven cases of the disease, only two occurred in females, and in both of these the valves were nearly quite sound in texture but the aorta being thinned and dilated, the valves could not meet so as to prevent regurgitation. None of the cases occurred in very early age. The youngest person presented laboring under the disease was 20 years of age. In this respect, inadequacy of the aortic valves differs from narrowing of the left auriculoventricular opening which is not infrequently met with in children, and even in infants at the breast. The causes of the disease are uncertain. In one case the disease followed an attack of acute rheumatism which had been accompanied by symptoms of pericarditis. In some cases the commencement of the disease was referred by the patient to an inflammatory affection of the chest, which had occurred months or years before, while in other cases no cause or date could be assigned.

The symptoms accompanying its commencement and progress are very variable. Most generally the patient describes the first sensations as having been a feeling of oppression and straitness across the chest with palpitation of the heart on unusual exercise. These symptoms become gradually more distressing, and are after a very uncertain period of time accompanied by fits of coughing resembling paroxysms of asthma, and terminating in scanty expectoration. In a few cases, however, cough was not at any time, even up to the last hours of life an urgent symptom. The oppression and straitness of the chest, with palpitation on any exertion, and an anxiety for a supply of fresh air being the principal complaints. As the disease proceeds, the straitness and oppression about the chest become more distressing, fits of coughing more frequent, and the patient has an anxiety, approaching to agony, for a free supply of fresh air, frequently starting from bed at night under the dread of suffocating. In the last stage the state of suffering is extreme. The patient will not lie down for a moment, from the dread of suffocation. The face which had been pale becomes purple on the lips as in suffocative catarrh, edema of the legs comes on, followed ultimately by edema of the hands and arms, there is no sleep, or there are almost incessant startings from it, the countenance assumes a most painful expression of sinking, and the patient at length dies exhausted. The pulse in no case was under 80. It ranged from that to 110, and in every case it has been all through the disease (unless influenced by medicine) full and vibrating, even to within a few hours of death.

The duration of the disease is very uncertain. No case was of less duration than two or three years, and some of the cases at present under treatment have been of seven or eight years' standing. The time which the disease may continue without terminating fatally seems to depend principally upon the extent to which regurgitation is permitted. The case in which the valves from small perforations allowed but little regurgitation continued for many years, while the case which furnished plate 2 and in which the valves were ruptured and much injured, allowing considerable regurgitation, terminated fatally in less than three years.

DIAGNOSIS

Inadequacy of the aortic valves may be confounded with narrowing of the mouth of the aorta, either congenital or from diseased valves, with disease of the auriculoventricular valves, with aneurysm of the arch of the aorta, or *arteria innominata*, with nervous palpitations and with asthma. Congenital narrowing of the mouth of the aorta is a very rare disease, but narrowing of the mouth of this vessel produced by vegetations on the valves is not unusual, and *bruit de soufflet* is a sign common to it, and to the disease we are considering. The resemblance between the signs of the two diseases extends, however, no further. The middle pulsation of the arteries arising from the arch of the aorta, which forms so striking a sign of inadequacy of the aortic valves is wanting in narrowing of the mouth of the aorta. The pulse is also strikingly different in the two diseases. In narrowing of the aortic orifice it is small and contracted, in inadequacy of the aortic valves it is invariably full and swelling. In narrowing of the aortic orifice there is generally a marked contrast between the pulse and the impulse of the heart. The pulse is small and contracted, the impulse of the heart is strong and energetic. In the disease we are considering when there is a contrast it is always in the inverse way, for while the arteries beat with violence, and the pulse is strong and full, the impulse of the heart is scarcely perceptible. When the initial valves becoming indurated or ossified produce narrowing of the auriculoventricular opening, that narrowing produces *bruit de soufflet*, and the *bruit de soufflet* thus produced might be confounded with the accompanying inadequacy of the aortic valves. Independently of the visible pulsation of the arteries and the state of the pulse, which accompany inadequacy of the aortic valves, stethoscopic examination points out with certainty the distinction of the two diseases. When the *bruit de soufflet* is produced by narrowing of the auriculoventricular opening it is heard loudest just where the impulse of the heart against the side is felt. In inadequacy of the aortic valves the converse holds. For over the point where the impulse is or should be felt, *bruit de soufflet* is either not heard at all or is heard very indistinctly, but as the stethoscope is moved upwards from the heart in a line corresponding

with the ascending aorta, the bruit de soufflet is heard growing louder and louder, until over the arch of the aorta, and in the large trunks arising from it, the sound grates upon the ear with harshness

Permanent patency of the mouth of the aorta may be mistaken for aneurysm. If the arch of the aorta and arteria innominata approach more nearly than usual to the notch of the sternum, the visible pulsation at the root of the neck becomes so prominent as to lead to a supposition that there is aneurysm, and even of a considerable size, at this part

Very lately a case came under my observation in which there was a remarkable resemblance to aneurysm. So strong were the pulsations for years in the region of the arteria innominata that until the examination of the body after death there was never even a doubt expressed that the case was not aneurysm. The aorta was thinned and was dilated so much as to render the valves inadequate to their office and leave a permanent patency between them. The arteria innominata, the carotids and subclavians were also dilated beyond their natural size, thus increasing the appearance of the pulsation, but there was no trace whatever of aneurysm in the arteria innominata, such as had been supposed to exist there during life. An acquaintance with the disease under consideration and a knowledge of the fact that a violent throbbing at the root of the neck or notch of the sternum may arise from another cause than aneurysm will prevent the formation of a rash opinion on the cause of the violent throbbing

The two diseases, aneurysm of the aorta and inadequacy of the valves, may, however, be combined. The first cases that came under my observation presenting the signs of inadequacy of the aortic valves were cases in which the valves were rendered useless in this way, namely, by the mouth of the aorta sharing in the aneurysmal dilatation. These cases led me into an error, for meeting the signs of permanent patency of the aortic orifice in conjunction with aneurysm, I erroneously attributed to the aneurysm the signs which arose from the permanent patency (vide *Lancet*, Feb 7, 1829)

Palpitation of the larger arterial trunks, depending on derangements of the nervous system, will sometimes in their violence simulate the visible pulsation arising from inadequate aortic valves, and in females these palpitations will last not only for months but for years, and seem to justify an opinion that there is organic disease of the heart. The nervous palpitation is not, however, accompanied by bruit de soufflet and frémissement, and the absence of these two signs is conclusive as to the nature of the disease. Sometimes, however, more than one examination is required before pronouncing a positive opinion, for in a nervous patient, the alarm excited by the first examination will render the circulation hurried and irregular, and hence there may be in the carotid or

subclavian a momentary bruit de soufflet In making the examination it is, moreover, necessary that the edge of the stethoscope should not be allowed to press on the artery, because its pressure is sometimes sufficient in those cases to produce the sound When the bruit de soufflet and fremissement are only momentary no value should be attached to them In permanent patency of the aorta they are never absent

TREATMENT

There is no class of disease to which the scientific principles that guide modern medicine have been less applied than to diseases of the heart

With the idea of heart disease is too frequently associated the notion that such disease, without regard to its precise nature or its cause, requires the action and continued enforcement of measures calculated to exhaust strength and depress vital energy, and this error is sanctioned by the standard works on the treatment of heart disease

Instead of such treatment, the measures most beneficial are those which by strengthening the general constitution, will give a proportionate degree of vigor to the muscular power of the heart, and thus enable it to carry on the circulation in the absence of that assistance which it ought to receive With this view a generous and sufficient diet of animal and vegetable food should be advised, at the same time that an abstinence from those beverages, such as malt liquors, which increase much the mass of the fluids, should be enjoined It is not at all necessary that the patient should be prohibited from attending to his business or profession, provided that he do not devote to it so much attention as to produce debility And as there is among patients who have learned that they are afflicted with heart disease a universal dread of sudden death it is necessary to undeceive them on this point, and in the present instance it can be done with perfect safety, as the termination of the disease is never sudden

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Having laid down the plan of treatment proper to be adopted as far as it produces effects upon the system, and through it upon the heart, constituting a part of the system, it now remains to examine the propriety of employing in the disease a remedy such as digitalis, which produces a specific effect upon the heart, rendering its action slow and weak, and which in consequence of that effect is usually recommended in cases of heart disease in conjunction with the measures already deprecated In inadequacy of the aortic valves the pulse generally ranges from 90 to 110 After each contraction of the ventricle during the pause or interval of rest occurring between that contraction and the next following a quantity of blood is regurgitating into the ventricles The

danger of the disease is in proportion to the quantity of blood that regurgitates, and the quantity that regurgitates will be large in proportion to the degree of inadequacy of the valves and to the length of the pause between the contractions of the ventricle during which the blood can be pouring back. If the action of the heart be rendered very slow, the pause after each contraction will be long, and consequently the regurgitation of blood must be considerable. Frequent action of the heart, on the contrary, makes the pause after each contraction short, and in proportion as the pauses are shortened the regurgitation must be lessened. Instead, then, of regarding an increase of frequency in the action of the heart as an aggravation of the disease, it must be viewed, as we have already viewed hypertrophy of the heart, as a provision for remedying as far as possible the evil consequences arising from inadequate valves. To retard in such circumstances the action of the heart would be to do an injury. In every case of this disease in which digitalis has been administered it has invariably aggravated the patient's sufferings. The oppression has become greater, the action of the heart more labored, the pulse intermittent and very often dicrotic from the heart's being unable by a single contraction to empty itself, general congestion and dropsy if present have been increased, and in some instances bronchitis from congestion has been induced, the respiration became laborious, and the strength so much sunk that patients seemed almost moribund. From this state they only recovered by omitting the digitalis and being placed on stimulants. In no case of this disease did digitalis produce the slightest good effect, and in all, the patients while under its exhibition were always worse.

Although the cure of inadequacy of the aortic valves is out of the reach of medicine, a correct knowledge of the nature of the affection is not the less necessary. The patient is relieved from harassing treatment, that, however applicable in other cases of heart disease, is not alone useless but positively injurious in this. In other affections of the heart there is a constant danger of sudden death from pulmonary apoplexy or hemorrhage, which may be induced even by ordinary exertion, and such danger keeps the patient in a state of perpetual terror. In this disease, on the contrary, assurance may be given against any sudden termination, and the patient may be permitted not only to attend to his business or profession but may be assured that, in leading a life of business and tolerable activity, he is adopting the very best means of prolonging life. Under treatment such as recommended, it is astonishing what little uneasiness inadequacy of the aortic valves will produce—indeed, very often not so much as those organic affections or growths of the liver, which are nevertheless viewed by the profession and by patients with much less terror.

EXPLANATION OF PLATE

Fig 1—Reticulated valves *A, A, A, A*, openings produced by absorption in valves, through which blood regurgitated, these valves were slightly thickened

Fig 2—*A*, left hand valve, with opening through it large enough to admit goose quill, and ruptured from its connection with the aorta so that it flapped back into the ventricle, *B*, bony depositions on inner coat of aorta, *C*, middle and right hand valves thickened and contracted in their free edges, so that they could be separated only a short distance from sides of aorta

Fig 3—*A, A*, openings in valves, as in figure 1, produced by absorption, one of the openings in right hand valve being large enough to permit finger to pass through, *B*, middle valve, projecting downward, curled back and bound to the aorta by bony deposition, so that it was totally useless, *C*, bony deposition tying edges of middle and right hand valves together, and at same time gluing them to aorta

Fig 1

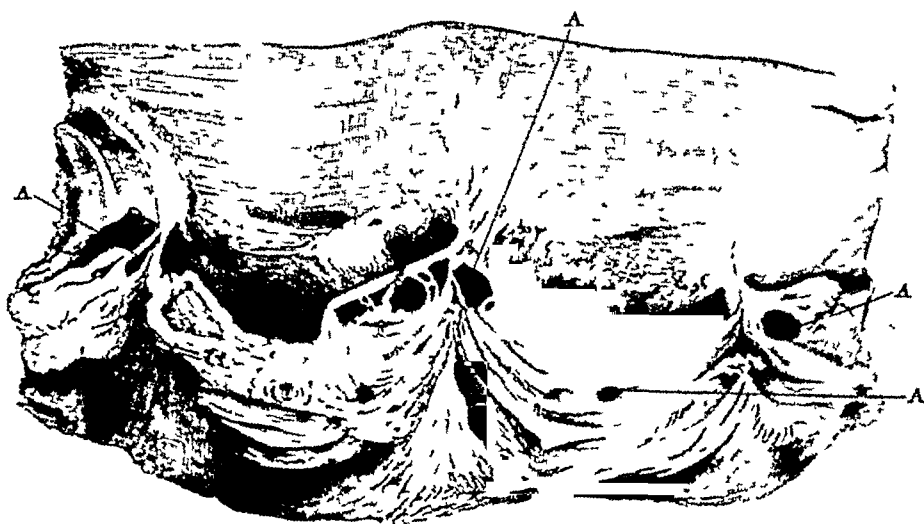


Fig 2

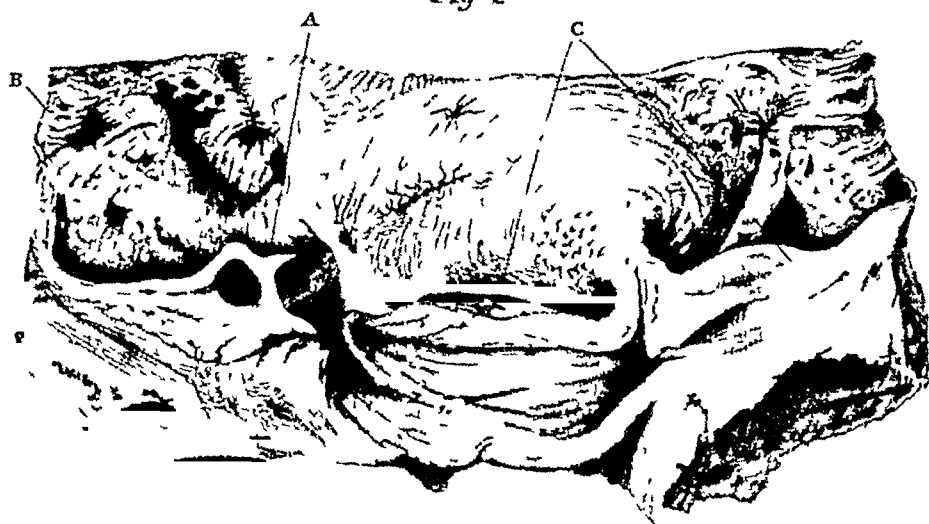


Fig 3



A CONFIRMATORY SIGN OF FREE FLUID IN THE PLEURAL SPACE

PRELIMINARY REPORT *

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The positive diagnosis of free fluid in the pleural space is difficult in some cases. Clinical observations on a series of patients seen during the last two and a half years have convinced me that the physical signs elicited high in the axilla of the affected side give information of value in the differentiation between free fluid and other conditions that may simulate it. In this series it was noticed that fluid was obtained on puncture in those cases showing the usual physical signs provided these signs were accompanied by dulness on percussion and a decrease in the intensity of the breath sounds high in the axilla of the affected side.

One group of cases showed signs that were taken to be those of an effusion. Examination high in the axilla revealed practically normal findings and on puncture no fluid was obtained. The underlying pathologic condition in this group was usually found to be a thickened pleura or an immobility of the diaphragm which so often accompanies and follows pulmonary and pleural disease.

Another group showed axillary dulness and signs in the back simulating free fluid, but the high axillary dulness was accompanied by exaggerated breath sounds. No fluid was obtained on puncture in such cases and the underlying condition was usually found to be a consolidation process.

Even slight dulness or a slight diminution in the intensity of the breath sounds is important because it was found that the amount of effusion is roughly proportional to the amount of dulness and change in the intensity of breathing high in the axilla. Slight dulness and slight diminution in breathing were observed with small effusions, while marked dulness and decided decrease in the intensity of the breath sounds were observed with large effusions. It was found important to examine *high* in the axilla and to refer and compare with the signs in "normal areas," comparison with the areas below the centers of the clavicles and with the axillary space of the opposite side being especially helpful.

* From the department of internal medicine, hospital division of the Medical College of Virginia

* Read before the Richmond Academy of Medicine, October, 1925

Mouriquand¹ in 1919 discussed the importance of axillary dulness in the diagnosis of pleural effusions, but did not mention the changes in the breath sounds. These changes are of importance because, as has been stated, dulness may also be present high in the axilla with lung consolidation as well as with fluid.

Ellis' line found in moderate effusions further substantiates the axillary dulness because the summit of the S shaped curve is found in the axilla. Dulness, however, occurs in many cases high in the axilla without the other component parts of Ellis' curve and, as has been stated, with a decrease in the intensity of the breath sounds. It is this change in the breath sounds that is sometimes almost diagnostic.

Cabot² says that "the position of the effusion depends only in part upon the influence of gravity, and is greatly influenced by capillarity and the degree of retraction of the lungs. Consequently the surface of the fluid is hardly ever horizontal. With the patient in an upright position it usually reaches a higher level in the axilla than in the back." From this statement it would seem that in the upright position at least, the high level of the fluid in the axilla would give rise to signs of fluid in this place. This conclusion conforms with the high axillary signs that have been observed in such cases.

The following cases illustrate the practical value of physical findings high in the axillary space.

REPORT OF CASES

CASE 1—*Pleurisy with effusion*

Miss M. B., aged 21, a nurse, on physical examination showed diminished expansion of the left side of the chest with Litten's sign absent on this side and present on the right side. The percussion note was flat from the angle of the scapula down and impaired above this mark. In front the percussion note was flat from the third rib down. Tactile fremitus was decreased in the flat areas, whispered voice was absent in the base and breath sounds were markedly diminished. High in the left axilla the percussion note was flat and breath sounds were distant. A diagnosis of free fluid in the left pleural sac was made and 1,300 cc. of straw colored fluid removed.

CASE 2—*Cardiac decompensation with bilateral hydrothorax*

B. H., a white man, aged 55, admitted for failing compensation of the heart, showed but little chest expansion and was flat from the interscapular areas down on both sides. The flat areas showed decreased transmission in the intensity of the breath and voice sounds. A diagnosis of bilateral hydrothorax was made on these findings. There was dulness high in both axillae, and there also was decreased transmission of the breath and voice sounds. The next day 740 cc. of a brownish fluid was removed from the right side of the chest, fluid was still running from the needle when the aspiration was discontinued. Three days later, the signs in the left chest being the same as on admission, aspiration of this side was done and 1,600 cc. of an amber fluid removed.

1 Mouriquand, Georges. Axillary Dulness in the Diagnosis of Pleural Effusions, *M. Press and Circ.* 159 No. 23 (Dec. 3) 1919.

2 Cabot, Richard C. *Physical Diagnosis*, Ed. 7, New York, William Wood & Co. 1922 p. 326.

CASE 3—*Pleurisy with effusion followed by chronic fibrous pleurisy (thick pleura)*

Mrs L D, a white woman aged 19, showed the classical signs of fluid in the left base, the flatness beginning at the scapula. The signs in the axilla confirmed the diagnosis of fluid. Seven hundred and fifty cubic centimeters of straw-colored fluid was then removed. The fluid reaccumulated and six days later 750 cc more was removed. Examination ten days later showed flatness in the base with dulness above reaching to the midscapular region. In this area tactile fremitus and whispered voice transmission decreased. These signs pointed either to more fluid or to a thick pleura in the base. A roentgen-ray report of the chest stated "it is probable that the pleural thickening contains a small amount of fluid." The percussion note was resonant high in the axilla and the breath sounds were of normal intensity. A needle was inserted into the flat area the next morning and no fluid was obtained.

CASE 4—*Small amount of free fluid*

T C, a man, aged 23, was admitted acutely ill. The temperature was 101 F, respiration, 36, and pulse, 120. The left lung showed the percussion note to be dull from the apex to the base, being almost flat in the base. The spoken voice and the breath sounds were decreased in intensity on the left from the midscapular area down. There were no râles, no rubs and no tubular breathing. The percussion note was resonant high in the axilla, and the breath sounds were well heard.

Twenty-four hours later a to-and-fro friction sound was heard on the left in the third and fourth interspaces in front. The signs in the back were the same except that the note now was definitely flat in the base. High in the left axilla the percussion note was found to be resonant but the intensity of the breath sounds decreased. The roentgenologist's report of roentgenograms taken on this day was that "appearances indicate a pneumonia involving the whole of the left lung." The clinical impression was that this was a case of lobar pneumonia with involvement of the pleura and that a small amount of fluid was present in the pleural sac. The signs in the base, however, were those of a moderate amount of free fluid. A needle was inserted in the back in the space below the angle of the scapula and only 15 cc of straw-colored fluid was found. Recovery took place gradually, the signs in the chest cleared up entirely, and the patient was discharged one month later in good health.

CASE 5—*Carcinomatosis with ascites and a small amount of free fluid in the pleural sac*

J W, a colored man, aged 31, showed a large irregular mass in the epigastrium and the general clinical picture of carcinoma of the stomach. In addition there was a marked ascites. The chest showed flatness behind on both sides, higher on the right, where it reached to the interscapular area. The bases showed a decrease in the intensity of the breathing and the transmission of the voice. These signs could either be due to fluid or to pushing up of the diaphragm by the ascites. The percussion note high in the right axilla was faintly dull, however, and the breath sounds questionably decreased in intensity. These signs pointed to a small amount of free fluid in the right pleural sac. The summit of the diaphragm on inspiration was seen by roentgenologic examination to reach the ninth rib in the scapular line. A needle was inserted into the eighth interspace and 25 cc of an amber, slightly turbid fluid withdrawn. No more fluid was obtainable. An exploratory laparotomy done eleven days later revealed a large carcinoma of the stomach with extensive metastases and a large amount of fluid free in the abdominal cavity. Metastases were felt with the finger on the diaphragm and it is likely that there were metastases to the pleura, this would account for the fluid in the pleural sac.

CASE 6—*Spontaneous pneumothorax*

William T, a white man, aged 42, was admitted very cyanotic, orthopneic and prostrated. The temperature was 104 F, and the pulse, 130. There was

marked impairment of the percussion note in the entire right side of the chest, the note, however, was not definitely flat. Tactile fremitus was absent on the right and the spoken voice and the whispered voice were not heard. There were no râles and no friction sounds. On account of the fever and a white blood cell count of 20,400 cells per cm it was thought that an empyema was present. There was no tympany in front or back. The patient had been sick for seven weeks and had been bringing up purulent sputum. High in the axilla on the right there was an impaired percussion note which was, however, tympanitic, and there were no breath sounds. A needle was inserted at the angle of the scapula, no fluid was obtained. The roentgenologist's report of roentgenograms taken later in the day stated that the "patient has a total collapse of the right side. The heart and mediastinum are displaced to the left. There appears to be a pneumonia involving the left lung." The next day the patient died.

CASE 7—*Pneumonia*

R. B., a colored man, aged 29, was admitted suffering with lobar pneumonia of both lobes on the left side. Two days after admission the left base was flat and the breath sounds were not heard, while above, in the interscapular area, the percussion note was dull and the breath sounds tubular. Anteriorly, in the apex, the percussion note was hyperresonant, below the third rib many crepitant râles were heard. High in the axilla the percussion note was resonant and crepitant râles were heard.

The patient had been acutely ill for nine days prior to admission, he appeared to be getting worse, and in the base of the left side of the chest there were signs of either fluid or a very thick pleura. A needle was therefore inserted in the flat area behind, but no fluid was obtained. The next day the patient died suddenly. Necropsy showed the right lung to be normal, the left was in a stage of resolution, both pleural sacs were free of fluid. The heart was markedly dilated, filled with blood and very flabby.

CONCLUSIONS

1 Dulness and decrease in the intensity of the breath sounds high in the axilla of the affected side is a confirmatory sign of free fluid in the pleural sac.

2 Dulness with an increase in the intensity of the breath sounds high in the axilla on the side that otherwise shows the classical signs of free fluid does not confirm this diagnosis, and is usually indicative of consolidation rather than of fluid.

3 This sign appears to be of value in differential diagnosis, especially between a thick pleura at the base and free fluid.

4 Interpretation of the findings high in the axilla is not puzzling, but the elicitation of the finer shades of dulness and decreased intensity of breath sounds is difficult and comparison with normal areas on the chest must be carefully made.

5 The amount of fluid present is roughly proportional to the extent and degree of dulness and of decrease in the intensity of the breath sounds high in the axilla.

6 The high level in the axilla of free fluid due to capillarity and the degree of retraction of the lungs forms the basis for the signs of fluid in the axilla.

BILIARY SYSTEM FUNCTION TESTS *

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My object in undertaking the work discussed in this article was to evaluate the tests for biliary function that have been advocated as being of practical help to the clinician in the diagnosis or prognosis of disturbances of the biliary system

A practical test of hepatic function must satisfy the following requirements

1 It must give information of a quantitative nature as to the functional capacity of any one element of the biliary system or of the biliary system as a whole

2 The technic of the test must be so simple that it can be carried out by any one familiar with laboratory methods

3 The performance of the test must require a minimal amount of time and equipment

The liver is a complex organ and has many functions to perform. The problem of finding any one test which throws light on all the functions of the liver or which determines the capacity of this organ to perform any one of its varied services is a difficult one. Moreover, tests used for estimating liver function may be influenced by factors outside the liver, such as obstruction of the bile ducts, changes in the circulation, and even by changes in the hemoglobin content of the blood, as this has been shown by Rous¹ to influence the excretion of bile.

A variety of different tests have been suggested for determining the functional activity of the liver and much work has been done in an effort to establish the clinical value of such tests. For example, Strauss² used levulose as a liver function test, while Bauer³ suggested galactose for the same purpose. A study of the value of nitrogen partition in the blood as a functional test for the liver was first undertaken by Chesney, Marshall and Rowntree⁴. Wilbur and Addis,⁵ as well as Einhorn,⁶

¹ From the medical clinic of the Peter Bent Brigham Hospital

^{*} This paper is No. 62 of a series of studies in metabolism from the Harvard Medical School and allied hospitals. The expenses of this investigation have been defrayed in part by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic disease.

1 Rous, P, and Drury, D R. J Exper Med **41** 601 (May) 1925

2 Strauss, L. Deutsche med Wchnschr **27** 757, 1901

3 Bauer. Wien med Wchnschr **56** 20, 1906

4 Chesney, A M, Marshall, E K Jr, and Rowntree, L G. J A M A **63** 1533 (Oct) 1914

5 Wilbur, R F, and Addis, Thomas. Arch Int Med **13** 235 (Feb) 1914

6 Einhorn, Max. More Practical Functional Tests of Liver, J A M A **81** 1494 (Nov) 1923.

have made use of urobilin and urobilinogen determinations in the urine. Whipple⁷ and his co-workers suggested the fibrinogen and the lipase tests for liver function, and Goodpasture⁸ suggested the fibrinolytic ferment test as an aid in diagnosing the liver cirrhoses. The value of the various methods mentioned above, most of which were introduced prior to 1914, has been discussed by Rowntree, Hurwitz and Bloomfield,⁹ by Krumbaar,¹⁰ and by Chesney, Marshall and Rowntree⁴ the general conclusion being that the tests suggested have been of limited practical value.

With the exception of Widal's¹¹ hemoclastic crisis test and the fat droplet (hemaconia) determination of Brulé,¹² the more recent methods have been dependent either on the excretion of a dye by means of the liver or on the determination of the bilirubin content of the blood serum. The use of the dye phenoltetrachlorophthalein was suggested by Rowntree⁹ in 1913. The dye was injected intravenously and the amount excreted through the liver in a unit of time was determined by quantitative studies of the feces. This test was modified by McNeil,¹³ who estimated the dye present in the bile after collecting it through a duodenal tube. Rosenthal¹⁴ further modified the method by following the retention of the dye in the blood rather than its excretion in the feces or in the bile. The use of other dye substances has been advocated more recently, e. g., rose bengal by Delprat and others,¹⁵ azorubins by Tada and Nakashima,¹⁶ and bromsulphalein by Rosenthal and

7 Whipple, G. H., and Hurwitz, S. H. *J. Exper. Med.* **13** 136, 1911. Whipple, G. H., Mason, V. R., and Peightal, T. C. *Bull. Johns Hopkins Hosp.* **24** 207, 1913. Whipple, G. H., Peightal, T. C., and Clark, A. H. *Bull. Johns Hopkins Hosp.* **24** 343, 1913. Whipple, G. H. *Am. J. Physiol.* **33** 50, 1914.

8 Goodpasture, E. W. *Bull. Johns Hopkins Hosp.* **25** 330, 1914.

9 Rowntree, L. G., Hurwitz, S. H., and Bloomfield, A. L. *Bull. Johns Hopkins Hosp.* **24** 327, 1913.

10 Krumbaar, E. B. *New York M. J.* **100** 719 (Oct.) 1914.

11 Widal, F., Abrami, P., and Iancovescu, N. *Presse med.* **28** 893 (Dec.) 1920.

12 Brulé. *Les recherches recentes sur les ictères*, 1919.

13 McNeil, H. L. *J. Lab. & Clin. Med.* **1** 822, 1916.

14 Rosenthal, S. M. *J. Pharm. & Exper. Therap.* **9** 385 (June) 1922, *New Method of Testing Liver Function with Phenoltetrachlorophthalein*, *J. A. M. A.* **79** 2151 (Dec. 23) 1922, *Proc. Soc. Exper. Biol. & Med.* **21** 2271 1923, *Phenoltetrachlorophthalein Test for Hepatic Function*. Recent Studies with the Author's Method, *J. A. M. A.* **83** 1049 (Oct. 4) 1924.

15 Delprat, G. D., Epstein, N. N., and Kerr, W. J. *New Liver Function Test, Elimination of Rose Bengal When Injected into Circulation of Living Subjects*, *Arch. Int. Med.* **34** 533 (Oct.) 1924.

16 Tada, Y., and Nakashima, K. *New Dye for Test of Liver and Biliary Tract Function, with Especial Reference to Its Clinical Use*, *J. A. M. A.* **83** 1292 (Oct. 25) 1924.

White¹⁷ Graham and Cole¹⁸ introduced a method of visualizing the gallbladder by means of the roentgen rays after the intravenous injection of an opaque medium. Several dyes, opaque to the roentgen rays, were tried by these investigators, who recommended the sodium salt of tetrabromphenolphthalein. Whitaker and Milliken¹⁹ demonstrated certain advantages of tetraiodophenolphthalein over tetrabromphenolphthalein for intravenous injection, while Whitaker, Milliken and Vogt²⁰ have been able to visualize the gallbladder after the oral administration of the iodo salt. Although certain toxic effects have been reported by those working with these dyes, there have been no fatalities reported and the method is being used with definite value in the diagnosis of gallbladder disease. Milliken and Whitaker²¹ report correct diagnoses by the intravenous method in 95 per cent of a series of twenty proved cases of gallbladder disease, while the clinical impression was correct in only 65 per cent of the same series.

For the determination of the serum bilirubin van den Bergh and Snapper²² made use of Ehrlich's diazo test. They found that when the diazo reagent (sulphanilic acid and sodium nitrite) was added to the blood serum of certain jaundiced patients a color reaction resulted, while in other cases the color was produced only after the addition of alcohol. Van den Bergh designated these reactions, respectively, the "direct" and the "indirect" reactions and believed that the "direct" reaction occurred only in cases of obstructive jaundice whereas the "indirect" reaction occurred as the result of jaundice of hemolytic origin. Lepehne,²³ McNee,²⁴ Andrews²⁵ and others have used the van den Bergh test clinically and have considered the "direct" and the "indirect" reactions to be of diagnostic value. Greene, Snell and Walters²⁶ question the diagnostic value of the "direct" and the

17 Rosenthal, S. M., and White, E. C. Clinical Application of Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84** 1112 (April 11) 1925.

18 Graham, E. A., and Cole, W. H. Roentgenologic Examination of Gallbladder. New Method Utilizing Intravenous Injections of Tetrabromphenolphthalein. *J. A. M. A.* **82** 613 (Feb 23) 1924. Graham, E. A., Cole, W. H., and Copher, G. H. Visualizing of Gallbladder by the Sodium Salt of Tetrabromphenolphthalein, *J. A. M. A.* **82** 1777 (May 31) 1924.

19 Whitaker, L. R., and Milliken, G. *Surg. Gynec. Obst.* **40** 17 (Jan.) 1925.

20 Whitaker, L. R., Milliken, G., and Vogt, E. C. *Surg. Gynec. Obst.* **40** 847 (June) 1925.

21 Milliken, G., and Whitaker, L. R. *Surg. Gynec. Obst.* **40** 646 (May) 1925.

22 Van den Bergh, A. A. H., and Snapper, J. *Deutsches Arch. f. klin. Med.* **110** 540, 1913.

23 Lepehne, G. *Deutsches Arch. f. klin. Med.* **135** 79 (Jan.) 1921, abstr., *J. A. M. A.* **76** 1051 (April 9) 1921.

24 McNee, J. W. *Quart. J. Med.* **16** 390 (July) 1923.

25 Andrews, C. H. *Brit. J. Exper. Path.* **5** 213 (Aug.) 1924.

26 Greene, C. H., Snell, A. M., and Walters, W. Diseases of Liver, Survey of Tests for Hepatic Function, *Arch. Int. Med.* **36** 248 (Aug.) 1925.

"indirect" reactions, but state that "enough is known of the indirect reaction as a quantitative measure of the serum bilirubin to assure its accuracy and reliability for clinical purposes" They have, however, suggested that the color quality of the standard solution and of the reaction in the unknown serum is not identical Blankenhorn²⁷ in 1917 suggested dilution of the blood plasma in order to determine the presence of increase in the bilirubin content of the blood, particularly in pernicious anemia Meulengracht,²⁸ also using plasma, suggested the use of an apparatus similar to the Sahli hemoglobinometer for comparison with a 1 10,000 potassium bichromate solution Gram²⁹ used serum in the place of plasma Maue³⁰ suggested the use of the Duboscq colorimeter for the color comparisons More extensive studies as to the clinical value of this method have been made by Meulengracht³¹ and by Bernheim³² Fouchet³³ suggested the determination of the intensity of the green color produced when the bilirubin of serum was converted into biliverdin by the addition of a dilute acid to the serum

It is evident from the foregoing rather brief discussion of the literature that a rather considerable amount of work has been done in studying tests of biliary function The great bulk of the more recent work has been centered on the clinical use of various dye substances in relation to biliary function and on the determination of the bilirubin content of the serum

Two tests were selected for this work from among the various tests enumerated above Rosenthal's¹⁴ modification of the phenoltetrachlorophthalein test and the so-called icterus index modified from the work of Blankenhorn²⁷ and of Meulengracht²⁸ As the results in both of these tests may be influenced by disturbances in the biliary system other than disturbances of the liver function it would seem advisable to speak of them as biliary system function tests rather than as liver function tests

DESCRIPTION OF METHODS USED

*Phenoltetrachlorophthalein Tests*³⁴—The technic as described by Rosenthal¹⁴ was followed in the use of the phenoltetrachlorophthalein test The test as used is

27 Blankenhorn, M A Pernicious Anemia, Arch Int Med 9 344 (March) 1917

28 Meulengracht, E Deutsches Arch f klin Med 132 285 (July) 1920

29 Gram, H C Ugesk f Læger 82 1137 (Sept 2) 1920

30 Maue, H P Surg Gynec Obst 34 752 (June) 1922

31 Meulengracht, E Ugesk f Læger 83 655 (May 19) 1921, Acta med Scandinav 53 827 (Jan) 1921, Ugesk f Læger 85 325 (May 10) 1923

32 Bernheim, Alice R Icterus Index (a Quantitative Estimation of Bilirubinemia), Aid in Diagnosis and Prognosis, J A M A 82 291 (Jan 26) 1924

33 Fouchet, A Compt rend Soc de biol 80 826, 1917

34 The disodium salt of phenoltetrachlorophthalein used in this work was obtained in 2 cc ampules from Hynson, Wescott and Dunning Each cubic centimeter of solution contained 50 mg of the dye

Five milligrams of the dye for each kilogram of body weight is given intravenously with approximately 150 cc of physiologic sodium chloride solution. This may be easily injected into one of the large veins of the arm by means of a 30 cc syringe and three-way stop cock. Small bore tubing is connected with the stop cock so that connections are made, respectively, with a needle introduced into a vein, a flask containing physiologic sodium chloride solution, and a syringe into which the proper amount of dye has been drawn. By proper adjustments of the stop cock the dye may be diluted with the saline solution and injected into the vein. Because of the loss of dye from leakage when the all glass syringes are used it is well to use a tight fitting Record syringe. Samples of 4 or 5 cc of blood are taken at intervals of fifteen minutes, one hour and two hours after the injection. As the dye may cling to the walls of the vein as well as to the needle or syringe, it is customary to withdraw blood from the other arm and with a different set of apparatus. The serum is then separated from the cells by centrifugalization and is removed by pipet to two 10 mm test tubes. To one of these tubes, which should contain approximately 0.8 cc of serum, is added 0.2 cc of a 5 per cent sodium hydrate solution in order to produce an alkaline medium in which the purple color of the dye develops. The concentration of the dye in the alkalinized serum is then determined by comparison with permanent standards³⁵. The comparison is made with the use of a simple comparator and direct daylight, using the tube of unalkalinized serum behind the tube of standard solution in order to make the medium of the alkalinized tube and the standard tube comparable. The figure obtained by such a comparison represents the amount of dye retained in the blood serum at the time of drawing the blood.

Icterus Index Test—The color of the blood serum due to variations in its content of bilirubin may be accurately recorded by comparison of the serum with a standard. This is the so-called icterus index test. Several methods have been suggested for such a comparison. The method described by Maue,³⁰ and subsequently by Bernheim,³² was used in the earlier part of the work, the technic of which is. A quantity of blood, approximately 5 cc, is withdrawn from an arm vein and is

35 Permanent standards for comparison may be prepared as described by Hogen (J Lab & Clin Med 8 619 [June] 1923) and Smith (Am J Obst & Gynec 8 298 [Sept] 1924). Ten milligrams of phenoltetrachlorophthalein is added to 100 cc of distilled water. This strength was suggested by Rosenthal as representing the approximate concentration that would be reached if all the injected dye remained in the plasma. We consider this standard as representing 100 per cent and prepare a series of standards in small uniform sized 10 mm tubes, ranging from 2 per cent to 30 per cent on the even numbers. To each tube 1 or 2 drops of 5 per cent sodium hydroxide solution is added in order to bring out the color. The tubes are then sealed and if kept in a dark place do not change color appreciably over a period of several months.

placed in a test tube. All apparatus used should be clean and dry in order to avoid hemolysis. The blood is allowed to stand at room temperature until retraction of the clot has occurred and is then centrifugalized with as little disturbance of the blood as possible. The serum is removed by means of a pipet and compared with a 1/10,000 solution of potassium bichromate in the cup of a colorimeter set at 15 mm. The depth of the standard, in this case 15, divided by the reading on the serum scale represents the icterus index of the serum. In highly colored serum it is necessary to dilute with physiologic sodium chloride solution in order to make the comparison. When the dilution is necessary the figure obtained by dividing 15 by the colorimetric reading will be multiplied by the dilution figure. By this method no attempt is made to determine the actual amount of bilirubin present, but, on the assumption that the color variation of the serum is due to bilirubin, the increase or decrease of pigment is indicated by comparison with an arbitrary standard. For clinical purposes such a determination should suffice provided there is sufficient evidence to indicate that the color variations are caused by changes in the bilirubin.

Author's Method of Color Comparison—In an attempt to simplify the test and to make it more universally available for clinical use, a method was introduced in which the color comparisons may be made without the use of the colorimeter. A series of standards are prepared with various dilutions of potassium bichromate. The dilutions are made to correspond with the colorimetric index figures as follows:

1/10,000 = 1	1/500 = 20
1/5,000 = 2	1/400 = 25
1/2,000 = 5	1/200 = 50
1/1,000 = 10	1/133 = 75
1/666 = 15	1/100 = 100

The solutions so prepared are kept in small test tubes of 10 mm diameter. One or two cubic centimeters of the serum to be tested is pipetted into a similar test tube, which is placed between two of the standard colors in a small comparator until a proper match is obtained. Direct daylight illumination is always used. The figure corresponding to the dilution that matches the serum is the icterus index of the serum. Readings between those of the standards may be estimated.

The method described above has in my series, proved simple to perform and in certain instances even more accurate than the colorimetric reading. Slight amounts of hemolysis or of clouding are often difficult to avoid even with the greatest care in obtaining serum. Such serum produces a color in the colorimeter that is difficult to distinguish from an increase of bilirubin. By means of the standards these changes appear quite distinct from the color changes produced by increased

bilirubin To avoid the clouding, blood should be taken when the patient is in a fasting state, preferably of five or more hours' duration

In case of any considerable degree of hemolysis some of the hemoglobin may be decolorized by the addition of a few drops of 3 per cent hydrochloric acid solution. An approximate reading may then be obtained. It has also been possible to extract the fat from cloudy serum with ether without an apparent alteration of the bilirubin.

TABLE 1—*Results in Cases Tested by Intravenous Injection of Phenoltetrachlorophthalein*

Case	Icterus Index	Per Cent of Retained Dye in			Palpable Liver	Jaundice	Diagnosis Confirmed by	
		15 Minutes	1 Hour	2 Hour				
1	50	18	19	16	+	+	Postmortem	Cirrhosis of liver
2	40	12	13	8	+	+		Cirrhosis of liver
3	25	8	12	10	—	+		Cirrhosis of liver
4	20	8	12	8	—	+	Postmortem	Cirrhosis of liver
5	—	8	10	8	+	—	—	Cirrhosis of liver
6	18	8	6	4	—	—	Operation	Cirrhosis of liver
7	—	8	4	3	—	—	Postmortem	Cirrhosis of liver, spleno megaly
8	6	6	2	Trace	—	—	—	Cirrhosis of liver, spleno megaly
9	19	11	12	7	+	—	—	Cirrhosis of liver (?), chronic alcoholism
10	—	5	7	4	+	—	—	Cirrhosis of liver (?), gastric ulcer
11	50	10	9	5	+	+	—	Cirrhosis of liver (?), malignant disease of liver (?)
12	125	22	30	28	—	+	—	Catarrhal jaundice
13	125	20	18	14	—	—	Operation	Carcinoma of pancreas
14	56	16	14	12	+	+	—	Carcinoma of pancreas
15	50	6	10	8	—	+	—	Metastatic malignancy of liver and lung
16	75	10	12	10	—	—	—	Carcinoma of liver (?)
17	16	8	10	8	—	+	Operation	Cholelithiasis (common duct)
18	13	6	4	2	—	+	—	Cholelithiasis
19	12	7	—	Trace	—	—	Operation	Subacute appendicitis (cholelithiasis ?)
20	14	4	1	0	—	+	Operation	Hodgkin's disease
21	—	7	—	2	—	+	—	Carcinoma of pancreas, pneumonia
22	3	5	3	0	+	—	—	Carcinoma of liver (?)
23	5	4	Trace	0	—	—	Postmortem	Pellagra, cholelithiasis
24	8	7	2	Trace	—	—	—	Neurasthenia
25	6	2	Trace	0	—	—	Operation	Carcinoma of ovary
26	—	4	1	0	—	—	—	Myeloid leukemia
27	—	4	1	0	—	+	—	Pernicious anemia
28	8	5	1	0	—	—	—	Chronic nephritis
29	—	4	2	Trace	—	—	—	Chronic nephritis
30	—	4	1	0	—	—	—	Chronic nephritis
31	—	4	1	0	—	—	—	Chronic nephritis
32	—	4	2	0	—	—	—	Chronic nephritis
33	5	4	2	0	—	—	—	No disease
34 50	—	6	2	0	—	—	—	17 cases of diabetes mellitus showing maximum and minimum retention
		2	0	0				

OBSERVATIONS WITH THE PHENOLTETRACHLOROPHTHALEIN TEST

The results obtained by the use of the phenoltetrachlorophthalein test in fifty cases are shown in table 1. In this series dye retention not to exceed 6 per cent in fifteen minutes, 2 per cent in one hour and a trace in two hours is considered normal. The diagnosis used is that recorded in the clinical record of the case whenever possible confirmed by operation or at necropsy.

In eleven cases of biliary cirrhosis varying degrees of abnormal dye retention were found in all but one (case 8). In this case there was rather marked ascites with distention of the abdomen, making palpation difficult. After removal of 11 liters of ascitic fluid, the spleen was barely palpable while the liver edge could not be definitely felt. Jaundice was not present. A diagnosis of splenomegaly and biliary cirrhosis was made in this case. The clinical picture of case 7 resembled that of case 8. Rather marked ascites made palpation of the abdomen difficult. The spleen was palpable but the liver was not. Jaundice was not present. There was a history of prolonged alcoholism. A diagnosis of splenomegaly and biliary cirrhosis was made. Splenectomy was performed, at which time a biopsy confirmed the diagnosis of biliary cirrhosis, the liver being slightly enlarged. Dye retention in this case was slightly greater than in the normal group. In the other nine cirrhosis cases, there was little question as to the presence of liver disturbance. Although the phenoltetrachlorophthalein retention in these cases offered confirmatory evidence of liver disturbance, it did not aid in the differential diagnosis.

In four cases of obstructive jaundice due to other causes than cirrhosis (cases 12, 13, 14 and 17) the dye retention was high. Carcinoma of the pancreas accounted for the obstruction in two of these, one patient had catarrhal jaundice, while obstruction in the fourth case was caused by a stone in the common duct. Definite jaundice was present in all. As the other evidences of obstruction were quite definite, the test was of no diagnostic value.

In one case (case 15) in which metastasis to the lung and liver had occurred from a hypernephroma there was a moderate degree of dye retention.

Patient 16 became jaundiced ten days before admission to the hospital, at which time the liver was palpable but not nodular. Cholecystectomy had been done seven months before, with relief of symptoms at that time. The dye retention figure was moderately increased in this case.

In a case (case 18) diagnosed as having cholelithiasis, in which jaundice was present, there was no abnormal retention of dye.

In the other thirty-two cases of this series there was no evidence of abnormal dye retention. One case of pernicious anemia and seventeen cases of diabetes are included in this normal group. All these cases were well within the limits of normal dye retention. This observation does not support the findings of Piersol and Bockus³⁶ who report a dye retention slightly greater than their normal figure in three of four diabetic patients tested.

³⁶ Piersol G. M., and Bockus, H. L. Comparative Studies in Liver Function by Some of the Later Methods, *J. A. M. A.* 83: 1043 (Oct. 4) 1924.

One other case (case 20) occurring in the normal group warrants further comment. Because of unexplained jaundice and a history suggesting gallbladder disease, an exploratory laparotomy was performed. No stones or other obstructions were found. A few weeks later enlarged glands appeared in the cervical region and a biopsy diagnosis of Hodgkin's disease was made. The negative test should perhaps have prevented the exploratory operation although the cause of the jaundice is still unexplained.

These results confirm the general impression given by the reports of several observers³⁷ that little information of value, either as an aid to diagnosis or prognosis, is obtained from the use of this test. On the other hand, the test has been considered by these workers and others to show rather accurately the degree of obstruction present in the cases in which an undoubted pathologic condition exists. Rosenthal¹⁴ concludes that the figures obtained in his series "give an index of the functional capacity of the liver." Ottenberg and Rosen,³⁸ by retesting patients with common duct stone just prior to operation, were able to demonstrate in a few instances that the stone had been passed. The results of Rosenfield and Schneiders³⁹ in a series of tests on pregnant women confirm Rosenthal's conclusions. They also believe that it is of value as an index in the treatment of the toxemias of pregnancy. Smith³⁵ reports the test to be of value in differentiating between preeclamptic toxemia and the nephritic type in pregnancy, the retention of dye being more constant in the former. Boardman and Schoonmaker⁴⁰ concluded in part from their work on twenty-two cases of cholecystitis that "in the phenoltetrachlorophthalein test we have a valuable means of studying the functional activity of the liver." Although it has been possible to demonstrate varying degrees of liver or biliary tract dysfunction by means of the phenoltetrachlorophthalein test, little information was obtained in the series of cases reported above which was of considerable value either in the diagnosis or prognosis of the cases. It was also felt that the method was too technical and time consuming to be of practical clinical value.

37 Ottenberg, R., Rosenfeld, S., and Goldsmith, L. Clinical Value of Serum Tetrachlorophthalein Test for Liver Function, *Arch Int Med* **34** 206 (Aug) 1924. Greene, C. H. *Minnesota Med* **8** 142 (March) 1925. Rowntree, L. G. The Role of Liver Function Tests in Practice, *Proc Am A Phys*, May, 1925, abstr., *J A M A* **84** 1775 (June 6) 1925.

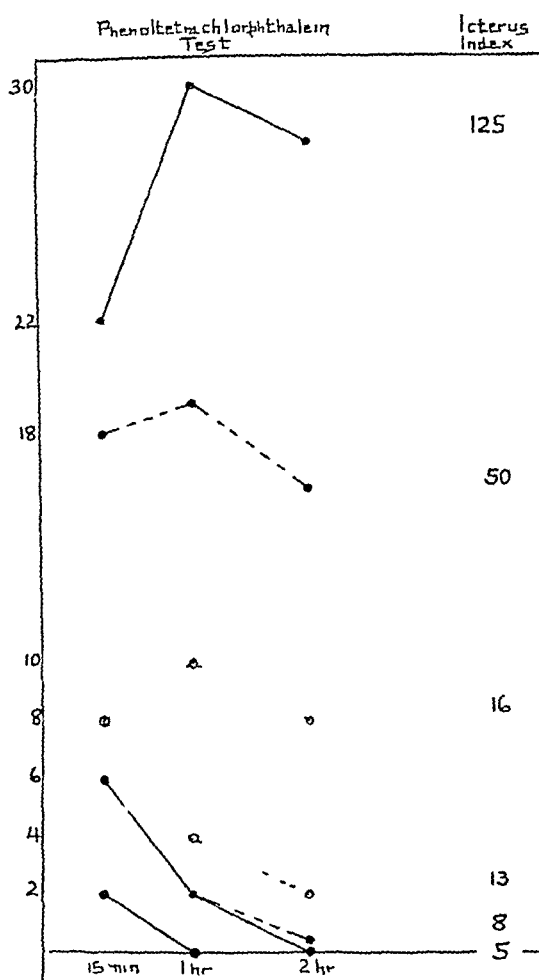
38 Ottenberg, R., and Rosen, S. Possible Application of Phenoltetrachlorophthalein Test to Obstructive Jaundice, *J A M A* **80**:1519 (May 26) 1923.

39 Rosenfield, H. H., and Schneiders, E. F. Improved Phenoltetrachlorophthalein Test for Liver Function in Pregnancy and Its Toxemias, *J A M A* **80** 743 (March 17) 1923.

40 Boardman, W. W., and Schoonmaker, G. D. *Am J M Sc* **168**:688 (Nov) 1924.

OBSERVATION WITH THE ICTERUS INDEX TEST

An estimation of the icterus index was made in many of the cases discussed in the foregoing. These figures are also included in table 1 and a few are shown in the accompanying chart along with the phenoltetrachlorophthalein curve obtained in the same case. They are shown here merely to compare results of the two methods and will be included



Comparison between phenoltetrachlorophthalein curve and icterus index in six representative cases: solid line (two lower), normals; solid line (upper), catarrhal jaundice; long dash broken line, cases of cirrhosis; and short dash broken line, cases of cholelithiasis.

in the icterus index tables. The information obtained by the use of this test in the preliminary series was quite as valuable as that obtained by the use of the more difficult and more time consuming phenoltetrachlorophthalein test. In many of these cases van den Bergh's test was also used by Evans.⁴¹ Little information was obtained by means of this test which was not available by the use of the icterus index determination.

41 Evans, J. A. Personal communication to the author.

Icterus index determinations made on 206 patients are recorded in this article. An index of 5 with a possible variation between 4 and 6 is considered normal.

Determinations were made on the serum of fifty-five patients without clinical signs of biliary system disease and in whom a normal index might be expected. The results are shown in table 2. Three indexes of this group were abnormal. One case of syphilis under treatment gave a reading of 8. As this patient was receiving intravenous arsenic at the time, there may have been slight liver damage although jaundice did not develop. In two instances the index was low, although there was not recorded any evidence of secondary anemia in the routine blood report of the ward.

In table 3 are shown the results of determinations made in forty cases of pernicious anemia. The index in these cases ranged from 5 up to 40.

TABLE 2—*Miscellaneous Group of Cases in All of Which a Normal Index Might be Expected*

Diagnosis	Number of Cases	Icterus Index
No disease	15	5
Syphilis	17	5
Syphilis	1	8
Syphilis	1	2
Nephritis (chronic)	3	5
Lymphosarcoma	2	5
Obesity	3	5
Osteomyelitis	1	5
Osteomyelitis	1	4
Acute infection	1	4
Carcinoma of ovary	1	6
Polycythemia	1	5
Purpura haemorrhagica	2	5
Pancreatitis	1	5
Intestinal indigestion	1	5
Hemiplegia	1	5
Hypertension	1	5
Endocervicitis	1	5
Multiple sclerosis	1	3
Total	55	

In thirty-five of the forty cases the index was above normal (50 per cent of these ranged between 10 and 20), while in five of the forty cases the index was normal. In these cases, although the blood changes were slight, a typical history, an absence of free hydrochloric acid in the gastric contents of three patients and in all characteristic neurologic changes justified the diagnosis. These five patients were all over 40 years of age at the time of onset of symptoms and in only one case (case 36) was the duration of symptoms longer than one and one-half years. The hemoglobin reading was above 70 per cent and the red cell count was above 3,000,000 in each case. These five patients (cases 36, 37, 38, 39 and 40) all had marked neurologic changes, which accounts for the fact that they came under observation during a remission. The other thirty-five were under observation because of symptoms directly referable to the anemia. Five cases (cases 6, 7, 27, 28 and 34) of the

series, in which a high index reading was obtained when the blood count was low, were kept under observation until the count became more nearly normal, at which time the index was recorded as normal in four cases and slightly below normal in the fifth. In all, then, ten cases of pernicious anemia tested during a remission gave a normal icterus index figure. These results confirm the reports of several others who have studied the serum color in pernicious anemia. Blankenhorn²⁷ reported twenty cases of pernicious anemia in which the Gmelin test for bile pigment was positive in sixteen. He concluded from his series that the cases with the highest bilirubin gave the most marked evidence of rapid blood destruction, as indicated by a high color index and loss of strength. Gram²⁹ concluded that the bilirubin rises as the patient gets worse in pernicious anemia. Maue³⁰ found only one case of pernicious anemia with an increased icterus index although he does not state how many

TABLE 3—*Determinations in Forty Cases of Pernicious Anemia*

Case	Icterus Index	Diagnosis	Case	Icterus Index	Diagnosis
1	40	Pernicious anemia	21	10	Pernicious anemia
2	35	Pernicious anemia	22	10	Pernicious anemia
3	35	Pernicious anemia	23	10	Pernicious anemia
4	30	Pernicious anemia	24	10	Pernicious anemia
5	30	Pernicious anemia	25	10	Pernicious anemia
6	30	Pernicious anemia	26	10	Pernicious anemia
7	25	Pernicious anemia	27	10	Pernicious anemia
8	25	Pernicious anemia	28	10	Pernicious anemia
9	25	Pernicious anemia	29	10	Pernicious anemia
10	25	Pernicious anemia	30	9	Pernicious anemia (combined sclerosis)
11	25	Pernicious anemia	31	9	Pernicious anemia
12	20	Pernicious anemia	32	9	Pernicious anemia
13	20	Pernicious anemia	33	9	Pernicious anemia
14	15	Pernicious anemia	34	8	Pernicious anemia
15	15	Pernicious anemia	35	7	Pernicious anemia
16	15	Pernicious anemia	36	5	Pernicious anemia (combined sclerosis)
17	15	Pernicious anemia	37	5	Pernicious anemia (combined sclerosis)
18	15	Pernicious anemia	38	5	Pernicious anemia (combined sclerosis)
19	12	Pernicious anemia	39	5	Pernicious anemia (combined sclerosis)
20	12	Pernicious anemia	40	5	Pernicious anemia (combined sclerosis)

were tested. Bernheim³² reported ten cases with indexes ranging from 6.5 to 12.5. The serum in which the index figure was 6.5 was taken during a remission. These various observations suggest, as might be expected, that during periods when blood destruction is going on the bilirubin content of the serum rises, while during a remission the serum color approaches normal.

Thirty-four cases showing evidence of secondary anemia are recorded in table 4. In all but six of these cases the icterus index was 4 or lower. The index determinations in these cases did not parallel either the hemoglobin or the red cell count. In several instances, however, the index became normal as the red cell count increased during convalescence following an acute fever, as occurred, for example, in case 7.

It is of interest to compare the figures in the last three tables (tables 2, 3 and 4) which suggest the value of the index test in the diag-

nosis of anemia. Of the normal group forty-three, or 78 per cent, had indexes of 5, while only three, or 5.6 per cent, had indexes that were above or below the possible normal variation of 4 to 6. In the anemia tables, although a few cases showed indexes running into the normal range, for the most part the range for the primary anemias was above normal while the secondary was below normal. Of the forty primary anemias thirty-five, or 87.5 per cent, showed an increased index, while of the thirty-four secondary anemias twenty-eight, or 82 per cent,

TABLE 4—*Determinations in Thirty-Four Cases Showing Evidence of Secondary Anemia*

Case	Diagnosis	Sex*	Per Cent Hemo globin	Red Cell Count	Icterus Index
1	Syphilis (secondary)	♂	80	5.0	3
2	Syphilis (secondary)	♂	75	4.5	3
3	Syphilis, duodenal ulcer	♂	80	4.5	2
4	Bronchopneumonia	♂	70	4.4	2
5	Syphilis	♂	65	4.3	3
6	Cause unknown	♂	75	1.2	5
7	Paratyphoid B fever	♂	70	4.2	2
8	Debility	♂	44	4.2	4
9	Syphilis, duodenal ulcer	♂	70	4.0	2
10	Cause unknown	♂	60	4.0	5
11	Debility	♂	60	4.0	5
12	Syphilis, duodenal ulcer	♂	70	3.7	1
13	Syphilis (secondary)	♂	63	3.7	3
14	Carcinoma of rectum	♂	60	3.6	3
15	Renal calculus (hemorrhage)	♂	56	3.6	1
16	Carcinoma of liver (metastatic)	♂	50	3.6	3
17	Endocarditis (rheumatic)	♂	70	3.5	1.5
18	Acute infection	♂	56	3.5	4
19	Cause unknown	♂	55	3.5	3
20	Banti's disease (?)	♂	40	3.5	2
21	Lymphosarcoma, syphilis	♂	56	3.4	2
22	Chronic hemorrhage	♂	50	3.2	3
23	Carcinoma of stomach	♂	45	3.0	5
24	Lymphosarcoma	♂	40	2.9	3
25	Carcinoma of stomach	♂	50	2.8	2
26	Hypernephroma	♂	50	2.6	2
27	Carcinoma of intestine	♂	40	2.5	2
28	Splenic anemia	♂	25	2.4	3
29	Duodenal ulcer (hemorrhage)	♂	40	2.3	3
30	Leukemia (atypical)	♂	41	2.0	5
31	Myeloid leukemia, aleukemia	♂	25	2.0	3
32	Splenic anemia	♂	24	1.7	5
33	Purpura haemorrhagica (hemorrhage)	♂	30	1.3	3
34	Aplastic anemia	♀	26	1.1	3

In this table thirty-four cases are recorded in which the blood count or the blood morphology indicated a secondary anemia. The red cell counts are shown by figures representing millions per cubic millimeter. The cases are arranged in order according to the red cell count, starting with the highest count.

* In this and the following tables ♂ indicates male, ♀ female.

showed a decreased pigment content. Approximately 15 per cent of the cases of both types of anemia fall into the group of those which do not show the characteristic index figures. It will be necessary in this group to anticipate the diagnosis by means of the somewhat characteristic findings in each type. These are, however, in many cases not entirely definite. The presence of free hydrochloric acid in the gastric content has been shown by Levine⁴² to be a constant aid in ruling out a primary

⁴² Levine, S. A., and Ladd, W. S. Bull. Johns Hopkins Hosp. 32: 254 (Aug.) 1921.

anemia The absence of the acid, on the other hand, does not prove the presence of primary anemia

The next series of cases include the patients in whom there was a question of a pathologic condition of the gallbladder or bile duct As a matter of convenience in discussing this series, the cases have been divided into four groups as follows

Group 1 This group includes four cases in which the gallbladder has been removed with subsequent attacks of pain in the right upper quadrant The cases are shown in table 5

In case 1 the complaint of a severe attack of right upper quadrant pain in the absence of demonstrable jaundice was at first considered an hysterical manifestation as the patient was considered to be of a neurotic temperament She became quite definitely jaundiced during the morning after a high icterus index had been demonstrated Three days later the icterus index was lower but still well above normal At operation a common duct stone was removed

Patient 2 left the hospital without operative investigation of the common duct because of lack of proof of obstruction The index at

TABLE 5—*Cases in Which Common Duct Obstruction Was Suspected After Cholecystectomy*

Case	Icterus Index	Sex	Age	
1	40 25	♀	30	Common duct stone at second operation
2	17	♀	50	Adhesions, recent stone at second operation (?)
3	25	♀	65	Common duct stone (?), no second operation
4	4	♀	27	No recurrence of pathologic condition

this time was 17 Following a subsequent attack of pain with jaundice an exploratory operation was done in another hospital The operator found many adhesions about the common duct and felt that there was evidence that a stone had recently been passed

Patient 3 entered the hospital following an attack of pain with jaundice nine years after removal of the gallbladder The icterus index was 25 at this time Because of the rather convincing evidence of obstruction, operation was advised but the patient refused to have this done Three months after leaving the hospital this patient reported that there had been no further attacks of pain or jaundice This would suggest that if a stone were present it was passed just before her admission to the hospital

Patient 4 had her gallbladder removed but has since complained a great deal of distress in the right upper quadrant The index was not above normal and the patient has since begun to feel better

Group 2 This group (table 6) includes ten cases in which a pathologic condition of the gallbladder or bile duct was demonstrated The first six patients had a high index and at operation definite disease

was demonstrated. The sixth patient had had no recent attacks of pain and on admission had a normal index. During the next few days she had attacks of pain and the index then was 15. At operation no stones were found but there was an inflammatory reaction suggesting that a stone had recently been present in the common duct, probably recently passed. In the next three cases there had been no recent attacks of pain and the index was normal. Stones were found in the gallbladder at operation in each case. In the last case there had been no history of gallbladder disturbance. Gallstones were demonstrated at necropsy.

TABLE 6—Cases in Which Disease of the Gallbladder or Bile Ducts was Demonstrated at Operation or at Necropsy

Case	Icterus Index	Sex	Age	Diagnosis Made by			Diagnosis
				Operation*	Roentgen Ray	History	
1	75	♀	59	+	0	+	Common duct stone
2	35	♀	38	+	+	+	Common duct stone
3	30	♀	32	+	—	+	Pericholecystitis
4	16	♀	42	+	—	+	Cholelithiasis
5	10	♀	?	+	0	+	Cholelithiasis
6	15	♀	40	+	0	+	Common duct stone (?)
7	6	♀	66	+	+	+	Cholelithiasis
8	5	♀	50	+	—	+	Cholelithiasis
9	5	♀	36	+	0	+	Cholelithiasis
10	5	♀	60	+	0	—	Cholelithiasis

* In this table, + means positive diagnosis, —, negative diagnosis, and 0, observation not made.

TABLE 7—Cases Suspected of Having Gallbladder or Bile Duct Disease But Not Proved

Case	Icterus Index	Sex	Age	Diagnosis Made by			Diagnosis
				Operation	Roentgen Ray	History	
1	25	♀	34	0	—	+	Cholelithiasis
2	13	♀	40	0	—	+	Cholelithiasis
3	10	♀	39	0	—	+	Cholelithiasis
4	25	♀	56	0	0	+	Cholelithiasis
5	30	♀	52	0	?	+	Cholelithiasis (?)
6	18	♀	27	0	0	+	Cholelithiasis (?)
7	25	♀	32	0	—	+	No diagnosis
8	15	♀	40	0	—	+	No diagnosis
9	15	♀	40	?	—	+	Duodenal ulcer (large liver)
10	13	♀	28	0	—	+	Cholelithiasis (?)
11	12	♀	16	?—	—	?	Subacute appendicitis

There was roentgen-ray evidence of gallbladder disease in three of five cases so examined.

Group 3. In this group of eleven cases (table 7) the index was high in all. The first four had suggestive histories of cholelithiasis although roentgen-ray examination failed to demonstrate disease in the three cases so studied. In the other seven cases of the group, no satisfactory diagnosis could be made from the evidence at hand. Patient 6 was admitted to the hospital complaining of severe right upper quadrant pain occurring at intervals during a period of several weeks. There was a slight degree of jaundice present on admission. No severe pain

occurred during eighteen days under observation. During this time the index, which was high on admission, dropped to normal. Was this a case of catarrhal jaundice, with pain exaggerated by a neurasthenic person, or was the jaundice due to stone obstruction? In cases 7 and 8 no diagnosis was made although, especially in case 8, there was suggestive evidence of bile duct disease. A duodenal ulcer was demonstrated in case 9. At operation the liver was found to be enlarged, possibly owing to duct obstruction from pressure. Patient 11 had a "subacute" appendix removed but no mention was made in the operator's note as to the condition of the gallbladder or bile ducts. In five of the last seven cases of this group in which roentgenograms were taken no pathologic condition was recorded in the gallbladder region.

Group 4. In table 8 seven cases are shown in which gallbladder disease was seriously considered in the differential diagnosis, but was quite definitely ruled out. The index was normal in each case with the possible exception of case 1.

TABLE 8—*Cases Studied as Being Possible Gallbladder or Bile Duct Diseases*

Case	Icterus Index	Sex	Age	Diagnosis Made by			Diagnosis
				Opera- tion	Roentgen Ray	His- tory	
1	7	♀	?	0	—	?	Chronic indigestion
2	6	♀	30	0	—	?	Obesity
3	5	♀	23	0	—	?	Duodenal ulcer
4	5	♀	45	0	—	?	Duodenal ulcer
5	5	♀	52	0	0	?	No diagnosis
6	5	♀	65	0	—	?	Angina pectoris (?)
7	5	♀	26	0	—	?	Gastric ulcer (?)

A series of tests on a miscellaneous group of cases is shown in table 9. The figures shown here suggest a few interesting features of the icterus index test.

1. In general the higher figures were recorded in the cases having bile duct obstruction rather than liver damage, e. g., carcinoma of the pancreas and catarrhal jaundice.

2. Cases of chronic myocarditis with passive congestion of the liver show an index higher than normal. The presence of jaundice in most of these cases was questionable clinically and not in proportion to the icterus index figure.

3. The icterus index is an accurate and easy method of following the progress of cases with jaundice. This is especially true in the cases of catarrhal jaundice.

There is no reason to discuss these cases individually as the facts of importance are shown in the table. In the first two cases of carcinoma of the pancreas artificial drainage of the bile duct was accomplished after the first icterus index determination in each case.

TABLE 9—Icterus Index Determinations in Several Types of Biliary System Dysfunction

Period Between Tests*	Icterus Index	Diagnosis	Period Between Tests	Icterus Index	Diagnosis
9 days	{100}			125	Catarrhal jaundice
	{50}	Cirrhosis of liver	12 days	{125}	
	85	Cirrhosis of liver		{75}	Catarrhal jaundice
4 days	{57}		2 days	{64}	
	{19}	Cirrhosis of liver	3 days	{40}	Catarrhal jaundice
	50	Cirrhosis of liver		{25}	
13 days	{50}		4 days	{50}	
7 days	{25}	Cirrhosis of liver	7 days	{30}	Catarrhal jaundice
	{50}			{15}	
	50	Cirrhosis of liver (?)		45	Catarrhal jaundice
	50	Cirrhosis of liver (?)		30	Catarrhal jaundice
	45	Cirrhosis of liver		25	Catarrhal jaundice
	45	Cirrhosis of liver		8	Catarrhal jaundice
33 days	{20}		10 days	{125}	
	{40}	Cirrhosis of liver (?)	3 days	{90}	
60 days	{30}		10 days	{57}	Carcinoma of pancreas
	{30}	Cirrhosis of liver		{30}	
	18	Cirrhosis of liver (?)	22 days	{100}	
30 days	{17}			{30}	Carcinoma of pancreas
28 days	{8}	Cirrhosis, splenomegaly		80	Carcinoma of pancreas
	{8}			75	Carcinoma of pancreas (?)
	15	Cirrhosis of liver (?)		56	Carcinoma of pancreas (?)
	8	Cirrhosis of liver		50	Chronic myocarditis
	5	Cirrhosis, splenomegaly		30	Chronic myocarditis
	5	Cirrhosis of liver (?)		20	Chronic myocarditis
	110	Acute yellow atrophy		20	Chronic myocarditis
	50	Malignant disease of liver		15	Chronic myocarditis
	50	Malignant disease of liver		14	Chronic myocarditis
	40	Malignant disease of liver		10	Chronic myocarditis
	12	Malignant disease of liver		5	Chronic myocarditis
				5	Chronic myocarditis
				5	Chronic myocarditis
				5	Chronic myocarditis

* Period in days between determinations

CONCLUSIONS

1 Although the phenoltetrachloiphthalein test as modified by Rosenthal will give accurate information as to the amount of biliary system dysfunction where this is definite, it is not of practical value as a diagnostic aid, except possibly in relation to the complications of pregnancy. Information of equal or greater value may be obtained by means of the much simpler icterus index test.

2 The icterus index is of definite diagnostic value in distinguishing between the primary and the secondary types of anemia. The normal variation of the index is from 4 to 6. Figures above or below this should be considered abnormal.

3 Information of value may be obtained in cases in which obstruction of bile ducts occurs. If the obstruction is transient, blood for the test should be obtained within from twelve to twenty-four hours after the possible obstruction has occurred. In the absence of anemia, liver damage or duct obstruction the index should be normal. There is no

reason to expect an increase of bilirubin in the serum because of the presence of stones in the gallbladder

4 Determination of the icterus index by the method suggested gives an accurate but easy method of following the progress of a jaundiced patient

5 The icterus index test is a test of considerable practical value to the clinician. The information obtained is of quantitative value and is easily obtained with little technical skill, expenditure of time and apparatus

WATER METABOLISM

III DEHYDRATION FEVERS *

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The production of high fevers in animals by dehydration has been the subject of much discussion and the literature is full of reports of exceedingly contradictory results. While our knowledge of the behavior of dehydrated infants (inanition fevers), reinforced by reports of exceedingly high temperatures produced by this means in animals, leaves no doubt that the loss of the water reserve of the body is an exceedingly important factor in temperature control, these fevers have followed no regular rule. Their artificial production is uncertain and inexplicable on the basis of dehydration alone, and so many discrepancies have occurred that many observers have denied the existence of such fevers altogether, attributing the fevers that do occur to some uncontrolled factors in these experiments. The three most commonly mentioned factors are (1) impurities in the glucose used for dehydrating the animal (dextrins, acid elements, etc.), (2) free hydrochloric acid in the physiologic sodium chloride solution, and (3) impurities from the rubber tubing.

These studies originally undertaken to solve this problem have yielded definite results, which enable us not only to predict in advance the amount of dehydration which will take place under given stimuli, but also roughly when and how much of a rise in temperature will occur.

At the onset of the experiments it was evident that the factors mentioned above could be ruled out. Careful analysis of the dehydrating solutions used (dextrose and sodium chloride) showed no impurities, and repeated hydrogen ion estimations ruled out the acid factor. As an additional precaution huge batches of the reagents were made up each in a single large container, which lasted through the entire series of experiments. The tubing was washed for days in running water, and not changed during the series. In spite of these precautions, extreme variations in the temperature reactions occurred. In one experiment a rise in temperature to 120 would occur, and in the next no rise or but a slight one of 1 or 2 degrees. No connection between the degree of dehydration and the fever could be demonstrated. High fevers occurred in dogs which dehydrated freely and those which did not, also, slight rises took place in both classes.

* From the department of surgery, University of Illinois College of Medicine

* Read before the Institute of Medicine, Chicago, Feb 27, 1926

Studies of the amount of sugar or salt excreted and of the concentration of each in the blood also yielded negative results, and it was felt that metabolic factors could be eliminated as the dogs had no albumin or casts in the urine before the dehydration began and the blood chemistry appeared normal (p_H , urea, total nitrogen, creatinine and cholesterol)

In all this work we had overlooked the crucial point, that a dog's temperature is controlled by the evaporation of water from his tongue, as he has no sweat glands, and loses heat through the skin only by

TABLE 1—*Experiment 44*

Female dog, weighing 12 Kg, injected intravenously with 5 per cent sodium chloride at rate of 25 cc per kilogram per hour for ninety minutes

Time	Intake	Output	Loss	Loss per Kg	Albumin	Temperature
11 00	Injection begun					100.8
11 15	75	10			0	100.8
11 30	150	30			0	100.8
11 45	225	100			0	100.8
12 00	300	180			0	
12 15	375	275			0	101.4
12 30	450	385			0	101.8
12 45	450	460	10	1	Trace	102.6
1 00	450	610	160	12	+	103.0
1 15	450	665	215	18	++	103.5
1 30	450	720	270	22.5	+++	104.0
1 45 urine ceased	450	740	290	24	Clotted on heating	105.0

TABLE 2—*Experiment 35*

Female dog, weighing 10 Kg, injected with 5 per cent sodium chloride at rate of 25 cc per kilogram per hour for ninety minutes, mouth tied shut

Time	Intake	Output	Loss	Loss per Kg	Temperature
10 25	Injection begun				99.0
10 40	65	20			99.0
10 55	135	100			
11 10	190	160			99.8
11 25	260	220			100.2
11 40	320	300			101.5
11 55	375	100	25	2.5	102.8
12 15	375	435	60	6	104.0
12 30	375	475	100	10	110.0
1 00	375	520	145	14.5	110.0*
1 30†	375	530	155	15.5	110.0*
2 00					116.0

* Thermometer would not read above 110

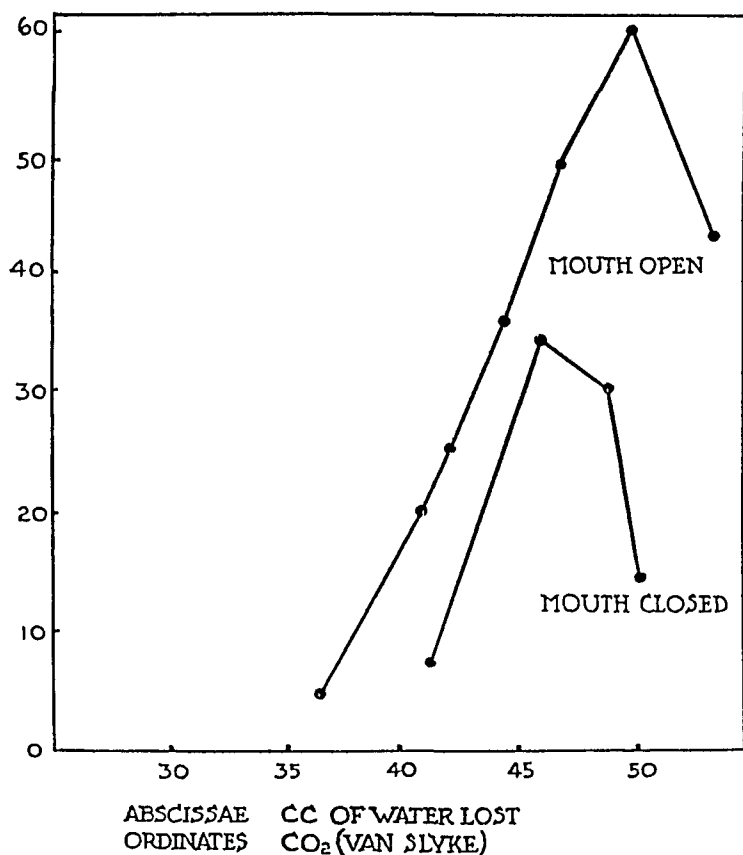
† Urine ceased

radiation. Therefore, the question of the ability of the dog to ventilate his tongue is a decisive factor. As dogs lie strapped to an operating table for these experiments, some will keep the mouth open and some closed, depending on whether the head hangs over the end of the frame. If the dog's mouth is allowed to stay open he can keep his body at fairly near normal temperature (101-105) even when extreme dehydration has been brought about as illustrated by experiment 44.

On the contrary if the dog's mouth is tied shut so that cooling off by the tongue is prevented, a more rapid rise in temperature takes place,

and in addition there is an extreme terminal rise of from 10 to 12 degrees (experiment 35)

Now in the whole series of experiments, the course of the rise in temperature is similar. In the moderate degrees of dehydration there is a slight rise (from 1 to 2 degrees) and as the limit of dehydration approaches, this increases to from 2 to 4 degrees. In no case were high fevers observed except as a terminal phenomenon. It can be shown that excretion of urine stops after the temperature has risen to 103-105. Albuminuria begins at 102 and at 105 is extreme and the flow ceases (experiment 44)



The course of any given experiment will then run as follows. The degree of dehydration possible can be predicted from the carbon dioxide, as shown in papers 1 and 2 of this series. This is true only if the dog is able to ventilate his tongue. During such an experiment the temperature will rise slowly from 2 to 4 degrees, at which point dehydration ceases and a terminal rise of 2 or 3 degrees more is likely. If the dog's mouth is tied shut at this period a terminal rise of from 10 to 12 degrees will occur. If, however, the dog's mouth is tied shut at the beginning of the experiment, the rise will be slightly more rapid and the failure of kidney function occurs a little sooner and the critical point (103-105) and extremes of temperature (116-120) are reached during the terminal stages.

It is clear that in a series of dogs with the mouth tied shut, the excretion would be less for any given carbon dioxide level. The accompanying chart shows the difference in the degree of dehydration possible in dogs with the mouth left open and with the mouth tied shut.

CONCLUSION

The unanimity of the pediatric literature in the belief in dehydration fevers is thus clear. Only the lower grades of temperature are there encountered, these, as I have shown, are always present in dehydrated animals. The experimental work done previously has given widely varying results which are due to fluctuations in the carbon dioxide, as shown in a previous article, and the presence or absence of a terminal extreme hyperpyrexia in these conflicting results can probably be attributed to the factor of the ventilation of the tongue.

A METHOD FOR THE CONTINUOUS QUANTITATIVE ESTIMATION OF GASTRIC SECRETION AND DISCHARGE IN MAN [†]

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The study of the pathologic physiology of the stomach has been hampered by lack of detailed knowledge of the normal motor and secretory activities of this organ. Animal experiments along the lines suggested by the ingenious work of Haidenhain and of Pawlow and their followers have, to be sure, laid down certain fundamental principles, but the results of the work can hardly be assumed to hold, as regards details, in man. Studies on human beings are to be found mainly in the literature of gastro-enterology and they have concerned themselves largely with the analysis of gastric contents following the ingestion of test meals of various sorts, their purpose has been to differentiate, if possible, various types of digestive disturbances and to lay down diagnostic criteria. Carlson and his associates have made important contributions to normal gastric physiology, without, however, investigating the wide variety of material that confronts the clinician.

Apparently no simple method is available at present for testing with reasonable completeness the secretory and motor response of the human stomach following a standard stimulus, the deficiencies of the familiar test meals may best be brought out by outlining the information that is necessary in order to have a satisfactory picture of gastric activity. In brief, an adequate test should possess the following qualifications:

- 1 The stimulus should be standardizable so that it may be applied repeatedly without being subject to variation.
- 2 The possibility, which always exists when a meal is ingested, of psychic stimulation or inhibition should be eliminated.
- 3 The admixture of saliva with the gastric contents should be avoided.
- 4 The regurgitation of duodenal contents must be controlled.
- 5 The procedure should yield a juice that is suitable for accurate chemical analysis.
- 6 One should obtain quantitative information about the fasting gastric secretion.

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7 One should obtain information about the total quantity of juice secreted during a given period as well as the hydrogen ion concentration and the total amount of acid

8 One should obtain information about the total volume of stomach contents at various intervals after the stimulation of secretion

9 One should obtain information about the amount of stomach contents which is discharged through the pylorus during various periods after stimulation

10 The material obtained from the stomach should be suitable for the titration of ferments

We have devised a simple procedure that seems to possess the foregoing qualifications. This article deals with a description of the method and with a summary of the types of information to be derived therefrom

METHODS

In every case the subject was examined while lying quietly in bed under what may be spoken of as basal conditions. The test was started at 2 p. m. and the only nourishment taken after the evening meal on the previous day was a cup of coffee at 6 a. m. No water was allowed for four hours preceding the examination. A duodenal tube was passed for a distance sufficient to let the tip reach the most dependent part of the stomach. The tube was then strapped to the subject's chin with adhesive tape and he was furnished with a basin into which all saliva secreted during the test was expectorated. The subject was made comfortable in a semi-reclining position. Immediately after the passage of the tube the fasting juice was aspirated. Suction was applied with the subject on his back and after he had turned on the right and on the left sides. This maneuver was repeated on all subsequent aspirations to be sure that the stomach was completely emptied. Five minutes after the first aspiration the fasting secretion was again aspirated. If bile was present, as occasionally happened, the aspirations were repeated at five minute intervals until clear juice was obtained or until the stomach remained empty. At this point and without attracting the subject's attention 50 cc. of 7 per cent alcohol solution to which had been added 0.5 cc. of 1 per cent phenolphthalein was injected through the tube. Within one to five minutes after the injection of this alcohol meal the gastric contents were completely withdrawn into a large graduated glass syringe, the total volume was noted, and the material was immediately reinjected with the exception of 10 cc., which was retained for analysis. As a rule the specimens were colorless and limpid and barring a few particles of mucus had the appearance of clear water. Ten minutes after the previous aspiration the contents were again completely withdrawn, measured, and reinjected with the

exception of 10 cc, which again was kept for analysis. The procedure was repeated at ten minute intervals until the stomach was empty. If more than 10 cc was present at the end of from sixty to seventy minutes the total contents were withdrawn and the test was terminated. The patients in no case complained of any discomfort due to the examination.

The fasting specimens and the samples retained from the subsequent aspirations were collected in paraffined graduated centrifuge tubes and the following examinations were made:

1 The amount and gross appearance of all the specimens were recorded.

2 In certain instances microscopic examination of centrifugated sediments was made.

3 The titratable acidity was estimated in terms of the number of cubic centimeters of tenth normal sodium hydroxid necessary to neutralize 100 cc of gastric juice. Dimethylamidoazobenzol and phenolphthalein were used as indicators since much of the work in the literature has been recorded in terms of them. With the former the end-point was taken to be the change from red to a frank yellow, with the latter the appearance of the first pinkish tint. Since we were dealing with a nonprotein test meal there usually was only a small difference between the readings with the two indicators.

4 Hydrogen ion concentration of the various specimens was determined by the colorimetric method. The procedure of Brown¹ enables one to make readings with small amounts of juice. Most of the values fell within the useful range of thymol blue, which has been shown to be satisfactory for work with stomach contents by Shohl and King² and which has been accepted by Clark³ as free from salt and protein errors. For hydrogen ion concentrations outside the range of p_H 1.2 to p_H 3.0 the following indicators were used:

Methyl violet	p_H 1.0-1.2
Bromphenol blue	3.0-4.6
Methyl red	4.4-6.0
Bromcresol purple	5.2-6.8
Bromthymol blue	6.0-7.6

5 The degree of dilution of the test meal by gastric juice was determined as follows. It has been mentioned that 0.5 cc of 1 per cent phenolphthalein was added to the test meal before injection. Parts of the fractions aspirated at ten minute intervals were made alkaline

1 Brown, J. H. *J. Lab. & Clin. Med.* **9**:3 (Jan.) 1924.

2 Shohl, A. T., and King, J. H. *Bull. Johns Hopkins Hosp.* **31**:158 (May) 1920.

3 Clark, W. M. *The Determination of Hydrogen Ion*, Baltimore, 1920.

with a few drops of 10 per cent sodium hydroxid solution in order to bring out the purple of the dye. The concentration of the phenolphthalein in the specimen was then estimated by making a reading in a colorimeter against a standard of the same concentration as the test meal. The decrease in concentration of phenolphthalein in successive specimens indicates the percentage dilution of the test meal by gastric juice at various time intervals.

6 The volume of gastric juice secreted in each ten minute period was calculated as follows. The total amount of juice in the stomach and the concentration of phenolphthalein at the beginning and end of each ten minute period were known. Decrease in phenolphthalein concentration could conceivably be brought about either by secretion of gastric juice, which would act as a diluent, or by secretion combined with discharge of stomach contents through the pylorus. In any case the maximum possible amount of juice secreted would evidently be given by the following formula

(1) $\left[\left(\frac{y}{x}\right) \times A\right] - A =$ maximum possible amount of juice excreted in ten minute period, in which

A = number of cubic centimeters of fluid in stomach at beginning of period,

x = concentration (percentage reading) of phenolphthalein at beginning of period, and

y = concentration of phenolphthalein at end of period

Similarly,

(2) $B - \left[\left(\frac{y}{x}\right) \times B\right] =$ minimum possible amount of juice secreted in ten minute period, in which x and y are as above and B = total amount of stomach contents (cubic centimeters) at the end of period

For example, if at the beginning of the period the stomach contained 37 cc. of material with a phenolphthalein concentration of 26 per cent, and if at the end of the period there was found to be 66 cc. of contents with a phenolphthalein of 13 per cent, then by formula (1) the maximum possible amount of juice secreted in the ten minute period was 37 cc. and the minimum possible amount was 33 cc. Obviously the actual amount secreted lies between these values.

In the protocols we have set down both the maximum and the minimum possible values, although an average of the two was used in calculating the amount of juice discharged from the stomach.

7 The amount of material discharged during each ten minute period was calculated by subtracting the total volume of stomach contents at the end of the period from the sum of the contents at the

beginning of the period and the amount of juice secreted. In the foregoing example $37 + 35 - 66 = 6$ cc (amount discharged)

8 The concentration of acid in the pure juice undiluted by test meal was calculated as follows. If, for example, the specimen aspirated from the stomach thirty minutes after the test meal has a phenolphthalein concentration of 30 per cent, then at this time 30 per cent of the stomach contents is made up of test meal and 70 per cent is gastric juice. If the titratable acidity of the specimen is 50 then the titratable acidity of the pure juice must be $71.4 \left(\frac{50}{70} \times 100 \right)$

9 In the titration of ferments the method we have used consisted in incubating at 37 C for one-half hour 1 cc of gastric juice with various quantities of normal human blood serum. The largest amount of serum digested as tested by precipitation with 20 per cent trichloroacetic acid was taken to represent the degree of peptic activity. This method and the results obtained with it will be discussed at another time.

Several workers⁴ have used procedures somewhat similar to the present one so far as a meal of weak alcohol to which phenolphthalein or another dye has been added is administered, and percentage dilutions of the dye are determined in samples aspirated at various intervals. These methods fail, however, to give the most important piece of information about gastric activity, namely, the volume of juice secreted and discharged. We have found that different persons may have the same percentage decrease in phenolphthalein when the amounts of juice secreted in the two cases represent the maximum and minimum extremes that may be encountered. This is, of course, due to the fact that dilution of dye depends not only on secretion but also on the rate of discharge.

The description of the foregoing procedure must be supplemented by a discussion of some difficulties and possible errors. In the first place it should be mentioned that a certain percentage of examinations—about 10 per cent—are vitiated by persistent regurgitation of bile after the test meal has been injected. If the examination is repeated at another time this difficulty is usually not reencountered. In the absence of visible bile staining it has seemed justifiable to assume that no duodenal regurgitation has taken place. A second possible source of error is incomplete aspiration of the stomach contents at the ten minute intervals. If only part of the juice is withdrawn the figures from which secretion and discharge are calculated will obviously be incorrect. Our impression is that by thorough suction applied with the subject on the right and left sides and in the dorsal position, all free fluid in the stom-

⁴ Heilmeyer, L. *Deutsches Arch f klin Med* **148** 273, 1925. Lanz, W. *Arch f klin Chir* **115** 294 (Feb.) 1921.

ach can be withdrawn. It is possible, however, that in certain instances of spasm, aspirations may be incomplete. The effect on gastric activity of withdrawing and reinjecting the stomach contents also is a matter for consideration, at any rate the present procedure approximates normal conditions more closely than complete drainage of the stomach at frequent intervals. Phenolphthalein has seemed quite satisfactory for measuring changes in concentration of the gastric juice. Colorimeter readings are readily made and the error is negligible. The dye is insoluble in acids and is not absorbed from the stomach.⁵ Prolonged contact with gastric juice *in vitro* produces no alteration in the colorimetric readings. The greatest difficulty that we have encountered has been in certain cases in which the estimation of the quantity of gastric secretion is unsatisfactory owing to wide differences between the calculated maximum and minimum amounts. As a rule the differences are so small that the correct figure can be closely approximated by an average, as may be seen in the succeeding protocols. Occasionally, however, accurate figures cannot be obtained and one can only tell in a general way the amount of gastric secretion. The alcohol test meal seems to be a satisfactory stimulus to stomach secretion, and we have confined ourselves to its use in order to get comparative results. It would be quite possible, however, to use other soluble substances in larger or smaller amounts.

RESULTS

Approximately 100 examinations have been made by the foregoing method. For the most part they have been made in the case of people without digestive symptoms. A good deal of information has been obtained about the variations that may occur in such a group. At the present time, however, only a few cases will be described in order to illustrate the method and to indicate the type of information that may be obtained.

PROTOCOLS OF EXAMINATIONS⁶

EXAMINATION 1—J. E., a normal boy, aged 19 years, had never had any digestive symptoms. He was examined Oct. 7, 1925, and again October 12. The results of the first test are shown in table 1 and chart 1, the results of the second test in table 2 and chart 2.

EXAMINATION 2—B. S., a normal boy, aged 15 years, had never had any digestive symptoms (table 3 and chart 3). It may be noted that this person secreted much more gastric juice than J. E., although the degree of acidity was somewhat less.

⁵ Sollmann. A Manual of Pharmacology, Ed 2, 1924, p. 208.

⁶ In the charts ordinates indicate amount of stomach contents and amount of secretion and discharge measured in cubic centimeters, and concentration of acid in terms of number of cubic centimeters of the tenth normal sodium hydroxide necessary to neutralize 100 cc. of pure gastric juice (phenolphthalein).

EXAMINATION 3—J S was examined twice (tables 4 and 5, charts 4 and 5). This man, aged 50, had a marked bradycardia. There were no digestive symptoms. It is of interest that in this case of anacidity as much juice was secreted as in some instances of persons with normal acid, for example by J E, on the second examination.

EXAMINATION 4—G W, a man, aged 49, was convalescent from bronchopneumonia. There were no digestive symptoms. The results of the test are shown in table 6 and chart 6.

EXAMINATION 5—P N, a man, aged 24, had had amebic dysentery several years before examination. At this time he was clinically well. There were no digestive symptoms (table 7 and chart 7).

EXAMINATION 6—I S was a neurotic man, aged 38 (chart 8 and table 8). There were vague digestive symptoms which may have been due to a duodenal ulcer.

EXAMINATION 7—A W, a man, aged 47, had hysteria. The results of the test in his case (table 9 and chart 9) should be contrasted with those in I S. Both men had a very low gastric juice, but I S secreted large amounts and retained fluid in his stomach, whereas A W secreted only small quantities of juice and emptied his stomach rapidly.

EXAMINATION 8—J C, a man, aged 35, convalescent from acute nephritis, had never had any digestive symptoms. Examination on two occasions (tables 10 and 11, charts 10 and 11) showed essentially the same result. There was an immediate great secretion of juice of low acidity followed by rapid emptying of the stomach and almost complete cessation of secretion.

EXAMINATION 9—M G H was a healthy woman, aged 28, the examination (table 12) showed the association of low acidity with hypermotility.

SUMMARY

A method is described whereby one may determine simultaneously the rate of gastric secretion and discharge, as well as other details of gastric function. The protocols given here illustrate the type of information that is obtained and indicate the useful possibilities of the method in studying the clinical pharmacology and pathology of the stomach.

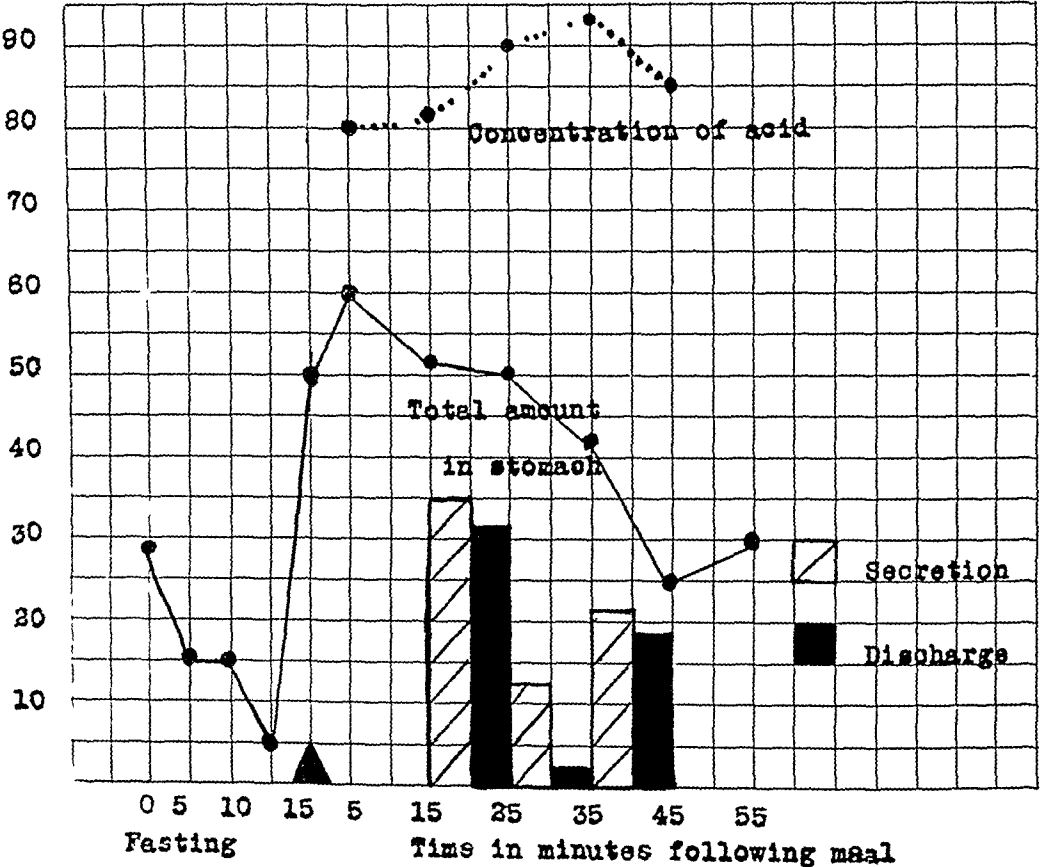


Chart 1—Findings in examination 1, test 1

TABLE 1—Results in Test 1, Examination 1

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Con- tents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concen- tration of Phenol phthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Dis- charged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl amidoazo- benzene	Phenol- phthalein	44					Maxi- mum, Cc	Mini- mum, Cc	Aver- age, Cc		
1	Fasting	29 cc faintly bile tinged fluid with small amount of mucus	1.6	14											
2	Fasting, 5 minutes after specimen 1	15 cc faintly bile tinged fluid with small amount of mucus	1.4	58			70								
3	Fasting, 10 minutes after specimen 1	15 cc colorless fluid with some mucus	1.3	80			92								92
4	Fasting, 15 minutes after specimen 1	5 cc colorless fluid with some mucus	1.2	87			99								99
5	5 min after meal	Clear, limpid fluid	1.45	30	32		60	11	49	60					80
6	15 min after meal	Clear, limpid fluid	1.25	54	56		73	13	40	71	45.5	26.0	35.7	31.0	81
7	25 min after meal	Clear, limpid fluid	1.20	68	70		50	10	40	23	13.6	13.0	13.3	13.0	90
8	35 min after meal	Clear, limpid fluid	1.15	78	80		42	9	33	14	25.0	17.0	21.0	19.0	93
9	45 min after meal	Clear, limpid fluid	1.10	80	84		25	11	14	71.1cc					85
10	55 min after meal	Heavily bile stained fluid					30								

J. I., a boy aged 19 years, Oct. 7, 1925 Diagnosis Normal control There were no symptoms of digestive disturbance

Total fasting contents

Fasting secretion during 10 minutes

Total secretion (30 minutes)

Largest amount secreted in 10 minutes

Largest amount in stomach during test

29 cc

From 20 to 30 cc

72 cc

35.7 cc

60 cc

Stomach "empty"

Lowest pH (45 minutes)

Highest free acid (45 minutes)

Highest total acid (45 minutes)

Highest acidity of pure juice (45 minutes)

55 minutes

1.10

80

84

93

Comment A high degree of acidity, gradual steady emptying of stomach over period of 55 minutes when bile regurgitated, no great volume of secretion in spite of high acidity, fasting secretion approximated that during test both in quantity and in acidity

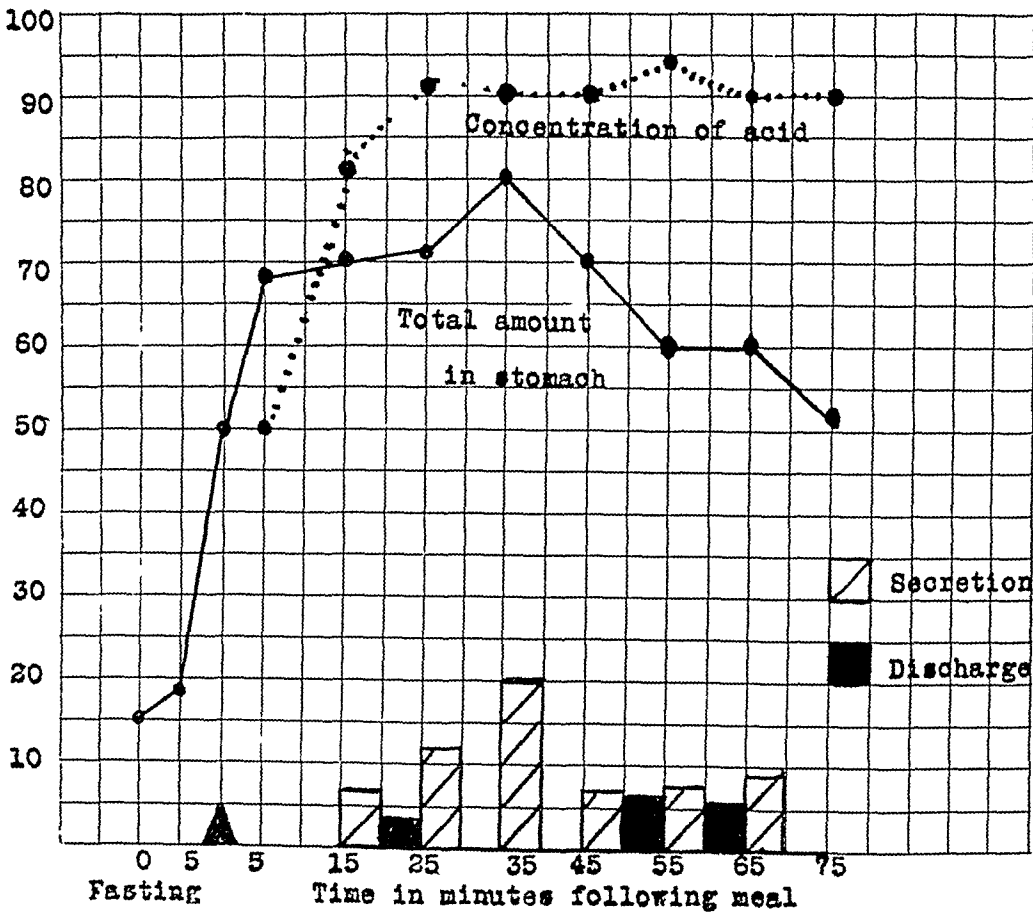


Chart 2—Findings in test 1, examination 2

TABLE 2—Results in Test 2, Examination 1

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Content, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl- amido- benzene	Phenol- phthalein	Phenol- phthalein					Maxi- mum, Cc	Mini- mum, Cc	Average, Cc		
1	Fasting	15 cc clear fluid with bits of mucus	1.60	26											
2	Fasting, 5 minutes after specimen 1	18 cc clear fluid with bits of mucus	1.45	34											
3	5 min after meal	Clear fluid with bits of mucus	1.30	24	30		68	10	58	40					50
4	15 min after meal	Clear fluid with bits of mucus	1.20	46	52		70	10	60	36	68	68		48	81
5	25 min after meal	Clear fluid with bits of mucus	1.20	56	64		72	12	60	30	120	120	120	0	91
6	35 min after meal	Clear fluid with bits of mucus	1.20	64	70		80 ?	10	70	22	200	200	200	0	80
7	45 min after meal	Clear fluid with bits of mucus	1.20	68	72		70	10	60	20	77	70	73	7	90
8	55 min after meal	Clear fluid with bits of mucus	1.15	72	78		70	10	60	17 ?	102	100	100	0	84
9	65 min after meal	Clear fluid with bits of mucus	1.15	74	78		62	10	52	15	78	78	78	6	91
10	75 min after meal	Clear fluid with bits of mucus	1.15	74	78		60			13	80	80	80	0	90

J E, Oct 12, 1925

Total fasting contents

Fasting secretion (5 minutes)

Total secretion (70 minutes)

Largest amount secreted in 10 minutes

Largest amount in stomach during test

Comment Findings somewhat different from previous examination, acidity high (about same as before), stomach emptied much more slowly and still contained 60 cc at 75 minutes, although quantity of juice secreted per 10 minute period was less than on previous examination

Stomach "empty" (still contained 60 cc at end of 75 minutes)

Lowest pH (55 minutes)

Highest free acid (65 minutes)

Highest total acid (55 minutes)

Highest acidity of pure juice

1.15

74

78

94

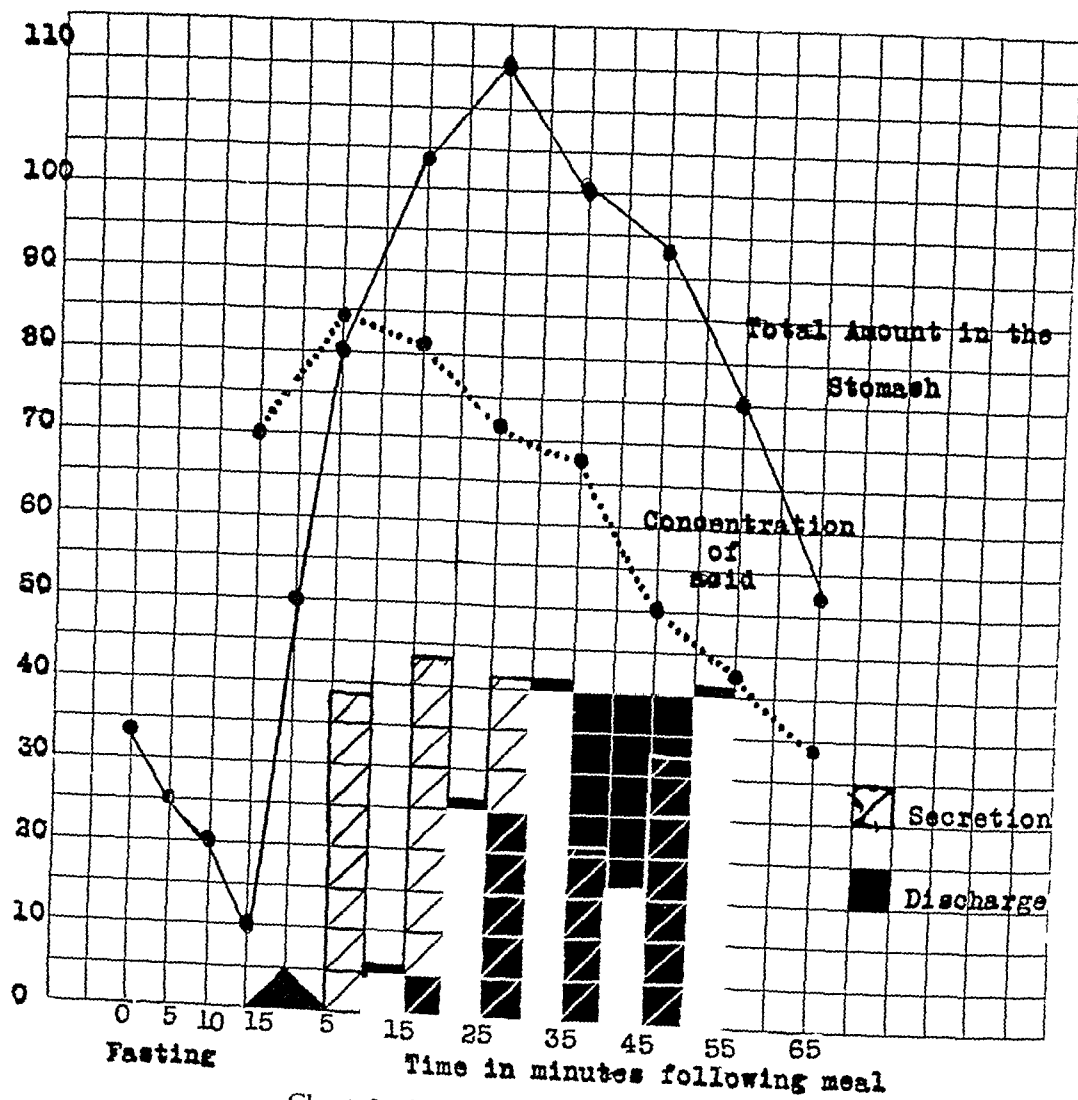


Chart 3—Findings in examination 2

TABLE 3—Results in Examination 2

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxide			Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl amidoazo benzenic	Phenolphthalein	Stomach					Maxim.	Minimum,	Average, Cc		
1	Fasting	31 cc deeply bile stained fluid		20	30										
2	Fasting, 5 minutes after specimen 1	25 cc slightly bile stained fluid with much mucus	1.7												
3	Fasting, 10 minutes after specimen 1	20 cc moderately bile tinged fluid with some mucus													
4	Fasting, 15 minutes after specimen 1	18 cc moderately bile tinged fluid with some mucus		60	70										70
5	5 min after meal	Clear, colorless fluid, some mucus	1.55	28	32	80	70	62	70						84
6	15 min after meal	Clear, colorless fluid, some mucus	1.45	46	50	104	10	39	91	39	40.6	39.0	39.8	5.8	81
7	25 min after meal	Clear, colorless fluid, some mucus	1.38	52	54	110	10	26	100	26	47.0	37.0	42.0	26.0	72
8	35 min after meal	Clear, colorless fluid, some mucus	1.40	50	56	100	10	17	90	17	50.0	33.0	41.5	41.5	67
9	45 min after meal	Clear, colorless fluid, some mucus	1.42	38	42	91	11	12	83	12	29.7	11.0	20.3	16.3	50
10	55 min after meal	Clear, colorless fluid, some mucus	1.50	34	40	75	11	8	64	8	41.5	25.0	33.0	41.0	43
11	65 min after meal	Clear, colorless fluid, some mucus	1.55	30	34	52		Trace							

B S., a boy, aged 15 years Diagnosis Healthy boy, normal control

Total fasting contents 34 cc
Fasting secretion during 10 minutes From 25 to 40 cc
Total secretion (50 minutes) 177 cc
Largest amount secreted in 10 minutes 42 cc
Largest amount in stomach during test 110 cc
Stomach "empty" (still contained 52 cc at 65 minutes)
Lowest pH (25 minutes) 1.38
Highest free acid (25 minutes) 52
Highest total acid (35 minutes) 56
Highest acidity of pure juice 84
Comment Titratable acidity high but not excessive pH did not fall as low as in many normal people, there was, however, an abundant secretion of juice, with increasing stomach content until 25 minutes and then a gradual emptying, the steady fall in acidity with decrease of secretion was of interest, fasting secretion was abundant and highly acid

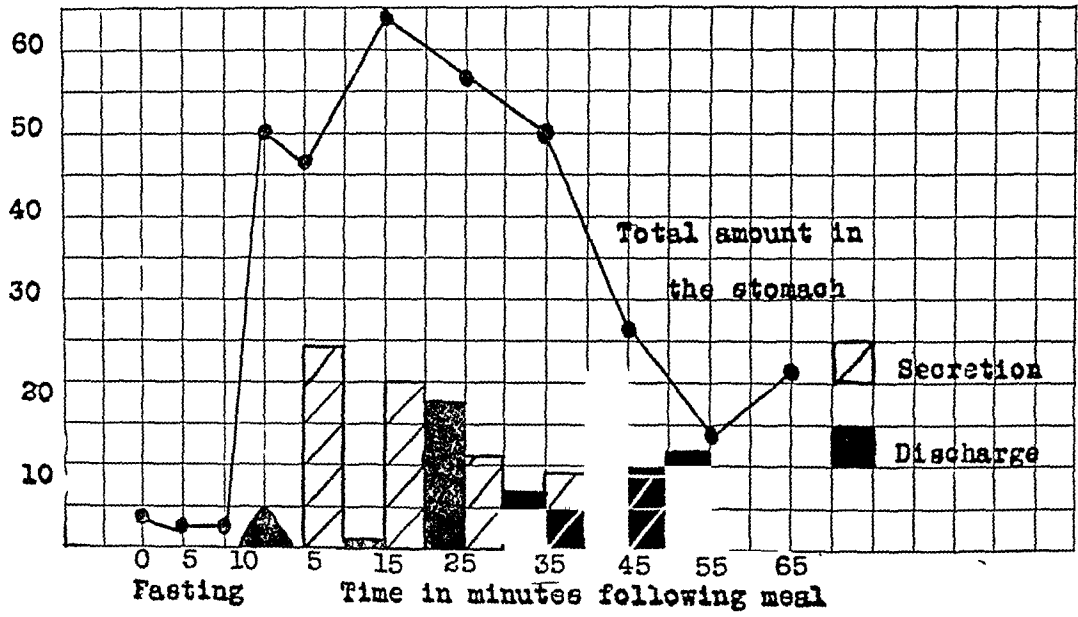


Chart 4—Findings in test 1, examination 3

TABLE 4—Results in Test 1, Examination 3

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl indolazo benzene	Phenolphthalein	Hydroxid					Maximum, Cc	Minimum, Cc	Average, Cc		
1	Fasting	4 cc practically pure mucus		0.0	2.0										
2	Fasting, 5 minutes after specimen 1	3 cc practically pure mucus	7.2	0.0	2.0										
3	Fasting, 10 minutes after specimen 1	2.5 cc practically pure mucus	7.1	0.0	2.0										
4	5 min after meal	Clear fluid with much mucus	6.9	0.0	2.0		46	6	40	83					
5	15 min after meal	Clear fluid with much mucus	6.6	0.0	4.0		64	11	53	50	26.5	23.5	24.5	1.0	
6	25 min after meal	Clear fluid with much mucus	6.5	0.0	4.0		56	10	46	35	22.5	17.0	20.0	17.0	
7	35 min after meal	Clear fluid with much mucus	6.4	0.0	4.0		50	11	39	28	11.5	10.0	11.0	7.0	
8	45 min after meal	Clear fluid with much mucus	6.6	0.0	4.0		26	7	19	21	13.0	5.5	9.5	22.0	
9	55 min after meal	Clear fluid with much mucus	6.6	0.0	4.0		14	8	6	14	9.5	4.5	7.0	12.0	
10	65 min after meal	Clear fluid with much mucus	6.7	0.0	4.0		22			Trace					

S, a man, aged 50, Oct 5, 1925 Diagnosis Bradycardia There were no symptoms of digestive disturbance

Total fasting contents	4.0 cc	Stomach "empty"	65 minutes
Fasting secretion during 10 minutes	5.5 cc	Lowest pH (35 minutes)	6.4
Total secretion (50 minutes)	72.0 cc	Highest free acid	0.0
Largest amount secreted in 10 minutes	24.5 cc	Highest total acid	4.0
Largest amount in stomach during test	64.0 cc		

Comment From standpoint of titratable acid, this case is one of complete anacidity, however, the pH falls to 6.4, which indicates some increase of acidity during test, there is a gradual steady emptying of stomach over period of 65 minutes, the total amount of secretion is relatively low, fasting secretion very scant

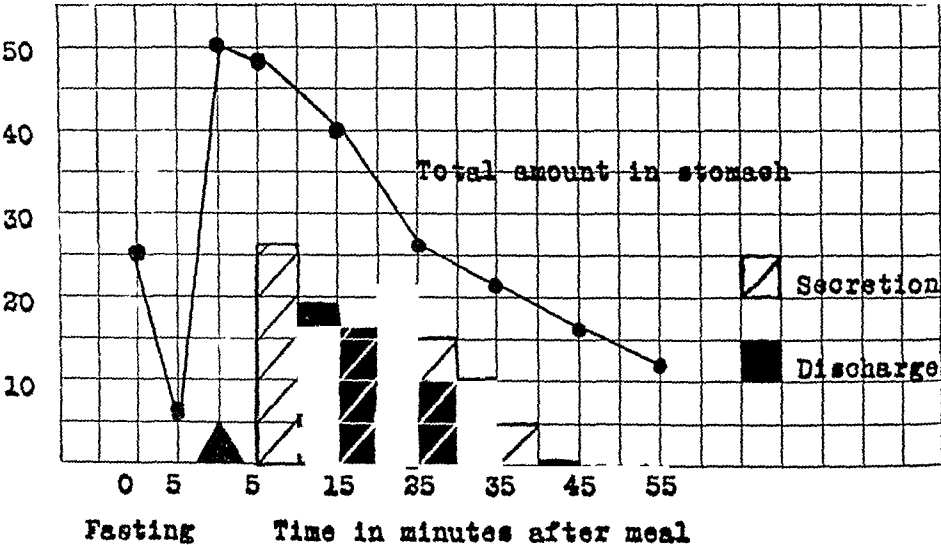


Chart 5—Findings in test 2, examination 3

TABLE 5—Results in Test 2, Examination 3

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl sulphato- benzene	Phenol- phthalein	Phenol- phthalein					Maxi- mum, Cc	Mini- mum, Cc	Average, Cc		
1	Fasting	25 cc turbid white fluid with particles of mucus	7.4	0.0											
2	Fasting, 5 minutes after specimen 1	6 cc turbid white fluid with particles of mucus	7.2	0.0											
3	5 min after meal	Clear fluid with bits of mucus	6.8	0.0			47	13	34	64					
4	15 min after meal	Clear fluid with bits of mucus	6.2	0.0			40	9	31	33	31.5	20.0	23.5	19.5	
5	25 min after meal	Clear fluid with bits of mucus	5.5	0.0			26	9.5	17.5	21	17.5	16.0	16.7	21.0	
6	35 min after meal	Clear fluid with bits of mucus	6.5	0.0			22	11	11	10	18.5	12.0	15.0	10.0	
7	45 min after meal	Clear fluid with bits of mucus	6.8	0.0			16	8	8	7	5.0	5.0	5.0	0.0	
8	55 min after meal	Clear fluid with bits of mucus	7.0	0.0			12			Trace					

S, Oct 11, 1925

Total fasting contents

Fasting secretion during 10 minutes

Total secretion (40 minutes)

Largest amount secreted in 10 minutes

Largest amount in stomach during test

Comment Findings essentially identical with those on previous examination

25 cc
12 cc
62 cc
27 cc
47 cc

Stomach "empty"
Lowest pH
Highest free acid
Highest total acid

15 minutes
5.5
0.0

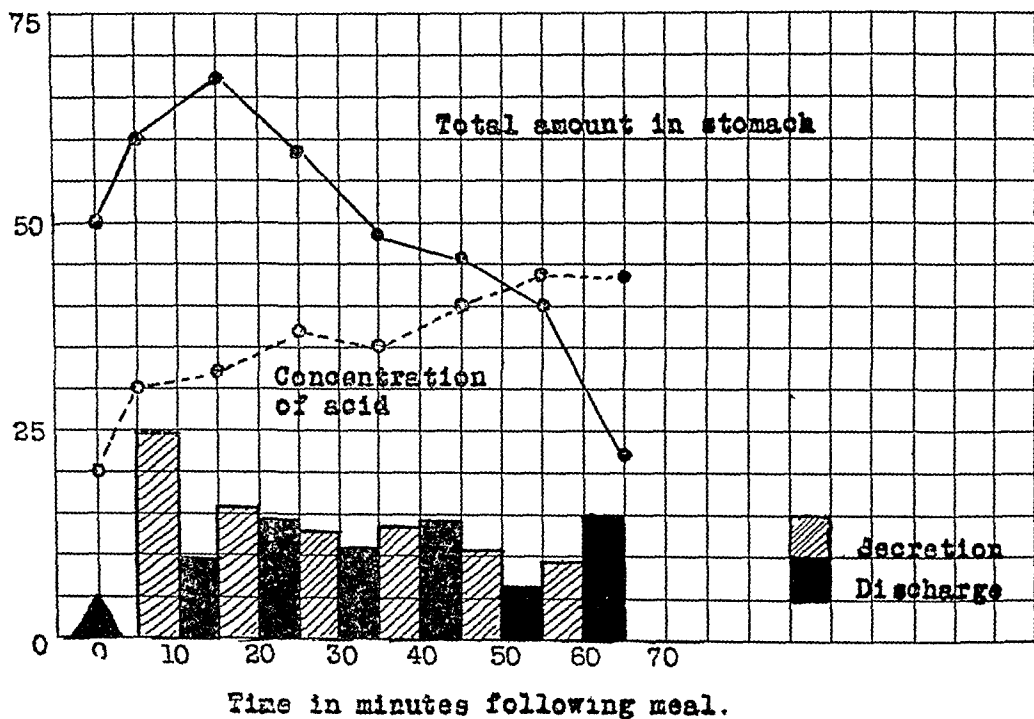


Chart 6—Findings in examination 4

TABLE 6—Results in Examination 4

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc. Tenth Normal Sodium Hydroxid			Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl amido-azo-benzene	Phenolphthalein	Phenol					Maxi mum, Cc	Mini mum, Cc	Average, Cc		
1	Fasting	Small amount of clear mucus													
2	Fasting, 5 minutes after specimen 1	7 cc clear mucus													
3	Fasting, 10 minutes after specimen 1	5 cc clear mucus													
4	Fasting, 15 minutes after specimen 1	5 cc clear fluid with mucus	2.05	10	20										20
5	5 min after meal	Clear, limpid fluid	2.10	6	10		60	8	52	65	26	23	24.5	9.4	30
6	15 min after meal	Clear, limpid fluid	1.95	11	17		67	10	57	44	16.5	14.0	15.7	14.7	32
7	25 min after meal	Clear, limpid fluid	1.80	18	24		58	12	46	34	13.8	12.0	13.0	11.0	35
8	35 min after meal	Clear, limpid fluid	1.70	20	26		48	11	37	26	13.3	13.0	13.0	14.0	40
9	45 min after meal	Clear, limpid fluid	1.65	23	33		46	11	33	19	12.2	11.0	11.6	7.0	43
10	55 min after meal	Clear, limpid fluid	1.60	30	37.5		40	12	28	14	11.0	7.0	9.0	15.0	42
11	65 min after meal	Clear, limpid fluid	1.55	32	38		22			10					

G W, a man, aged 49 Diagnosis Convalescent from bronchopneumonia, no digestive symptoms

Total fasting contents	A few cc	Stomach "empty"	65 minutes
Fasting secretion during 10 minutes	10 cc	Lowest pH (65 minutes)	1.55
Total secretion (60 minutes)	87 cc	Highest free acid (65 minutes)	32
Largest amount secreted in 10 minute period	24.5 cc	Highest total acid (65 minutes)	38
Largest amount in stomach during test	67 cc	Highest acidity of pure juice	

Comment Acidity of juice increased gradually and steadily but never reached a high value, the stomach emptied slowly and rather uniformly, at first a good deal of juice was secreted—the quantity in the ten minute periods steadily diminished, fasting secretions scanty and of low acidity

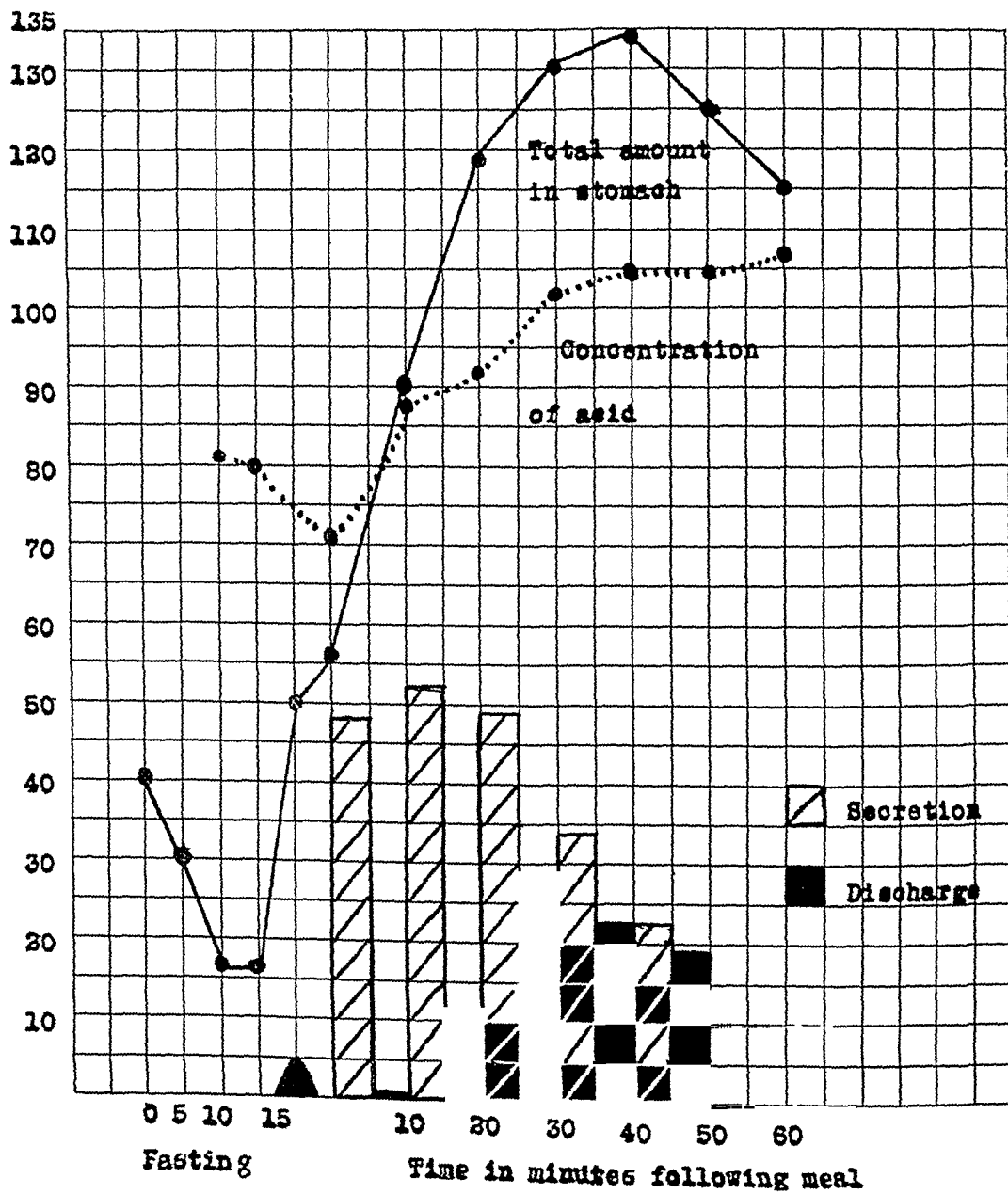


Chart 7—Findings in examination 5

TABLE 7—Results in Examination 5

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl-amidoazobenzene	Phenolphthalein	Stomach Contents, Cc					Maximum, Cc	Minimum, Cc	Average, Cc		
1	Fasting	40 cc bile													
2	Fasting, 5 minutes after specimen 1	30 cc moderately tinged fluid													
3	Fasting, 10 minutes after specimen 1	16 cc slightly bile tinged fluid	1.2	78	82										82
4	Fasting, 15 minutes after specimen 1	16 cc slightly bile tinged fluid	1.2	72	80										80
5	Immediately after meal	Clear, colorless fluid	1.9	16	20	56	13	43	72						71
6	10 min after meal	Clear, colorless fluid	1.25	50	58	90	12	78	34	47.3	47.3	47.3	0		57
7	20 min after meal	Clear, colorless fluid	1.15	70	74	118	9	111	20	54.6	50.0	52.0	12		92
8	30 min after meal	Clear, colorless fluid	1.10	78	88	130	10	120	13	54.5	44.0	49.0	28		101
9	40 min after meal	Clear, colorless fluid	1.10	84	94	133	11	122	10	36.0	31.0	33.5	22.5		104
10	50 min after meal	Clear, colorless fluid	1.05	88	96	125	9	114	8	24.4	21.0	22.5	19.5		104
11	60 min after meal	Clear, colorless fluid	1.05	94	102	115			1?						106

P N, a man, aged 24 Diagnosis Old amebic dysentery (inactive), no gastric symptoms

Total fasting contents

Fasting secretion during 10 minutes

Total secretion (50 minutes)

Largest amount secreted in 10 minutes

Largest amount in stomach during test

Stomach "empty" (still contained 115 cc at 60 minutes)

Lowest pH (50 minutes)

Highest free acid (60 minutes)

Highest total acid (60 minutes)

Highest acidity of pure juice

1.05

.94

.102

.106

Comment Prompt secretion of large amounts of highly acid juice, acidity increased steadily during experiment, whereas volume secreted diminished, discharge at first was much below secretion and volume of fluid in stomach rose to 133 cc and then decreased, fasting secretion abundant and highly acid

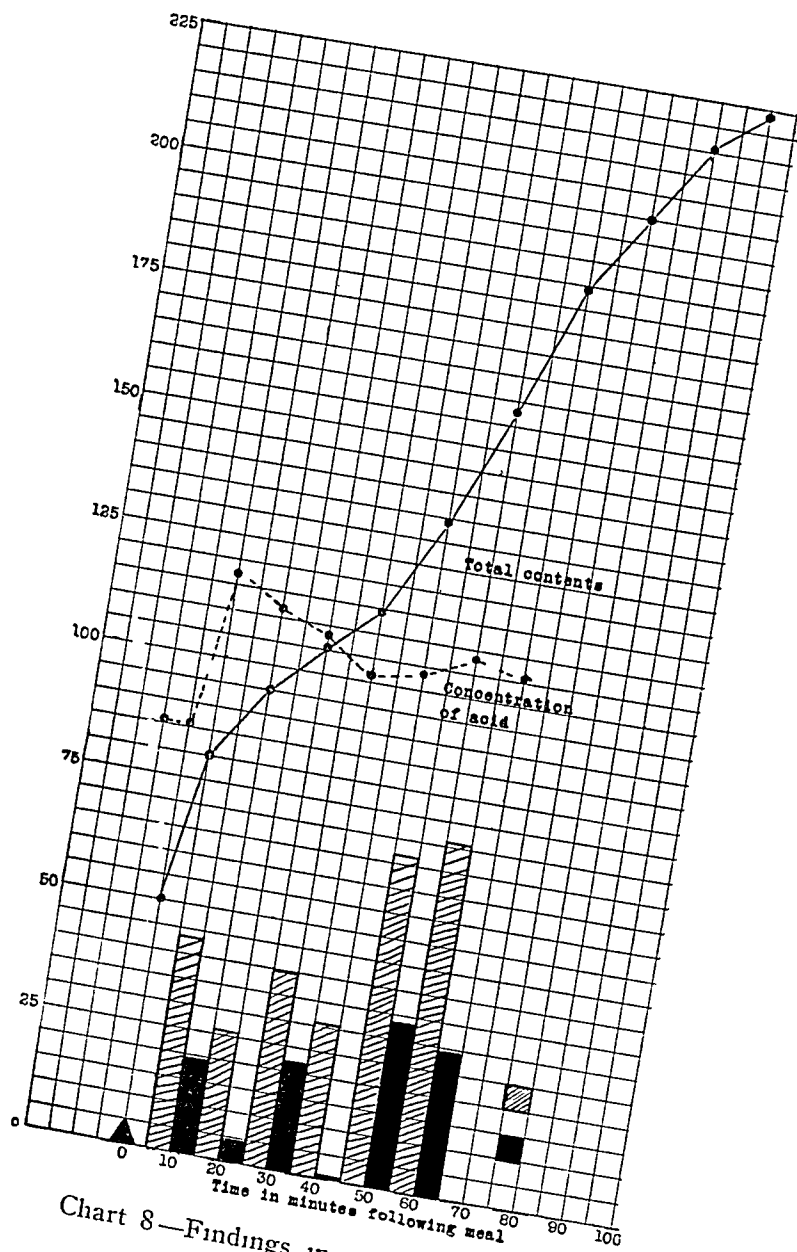


Chart 8—Findings in examination 6

TABLE 8—Results in Examination 6

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Ce tenth Normal Sodium Hydroxid			Total Stomach Contents, Ce	Specimen Retained, Ce	Amount Returned to Stomach, Ce	Concentration of Phenol phthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Ce	Acidity of Pure Juice
				Dimethyl amidoazo benzene	Phenol phthalein	Stomach					Maximum, Ce	Minimum, Ce	Average, Ce		
1	Fasting	70 cc clear fluid, slightly bile tinged	1.20	80	86										86
2	Fasting, 5 minutes after specimen 1	25 cc clear fluid, faint bile tinge	1.20	80	86										86
3	5 min after meal	Clear, limpid fluid	1.25	64	68	80	9	71	42						117
4	15 min after meal	Clear, limpid fluid	1.20	80	84	95	11	84	25					19	112
5	25 min after meal	Clear, limpid fluid	1.15	84	88	106	10	96	19		48.2	38.5	43.0	4	108
6	35 min after meal	Clear, limpid fluid	1.10	88	92	114	11	103	13		26.0	26.0	26.0	22	101
7	45 min after meal	Clear, limpid fluid	1.10	90	94	134	10	124	10		44.1	36.0	40.0	0	104
8	55 min after meal	Clear, limpid fluid	1.05	98	102	158	11	147	6		31.0	31.0	31.0	33	108
9	65 min after meal	Clear, limpid fluid	1.05	98	102	189	10	179	1		74.0	60.0	67.0	29	106
10	75 min after meal	Clear, limpid fluid	1.05	98	102	200	10	190	Trace		79.0	63.0	71.0		
11	85 min after meal	Clear, limpid fluid	1.05	98	102	216	11	205	Trace						
12	95 min after meal	Clear, limpid fluid	1.05	98	102	223			Trace						

I S, a man, aged 38 Diagnosis Gastric neurosis, duodenal ulcer ?

Total fasting contents 50 cc
Fasting secretion during 10 minutes 50 cc ?
Total secretion (60 minutes) 2.8 cc
Largest amount secreted in 10 minutes 67 cc
Largest amount of juice in stomach during test 223 cc

Stomach "empty" (still 223 cc of 95 minutes)

Lowest pH (55 minutes) 1.05
Highest free acid (55 minutes) .98
Highest total acid (55 minutes) 102
Highest acidity of pure juice 117

Comment Prompt secretion of large amounts of very acid juice which decreased somewhat in acidity but increased in amount as test progressed, only slight discharge so that large amount of fluid accumulated in stomach, fasting secretion abundant and very acid

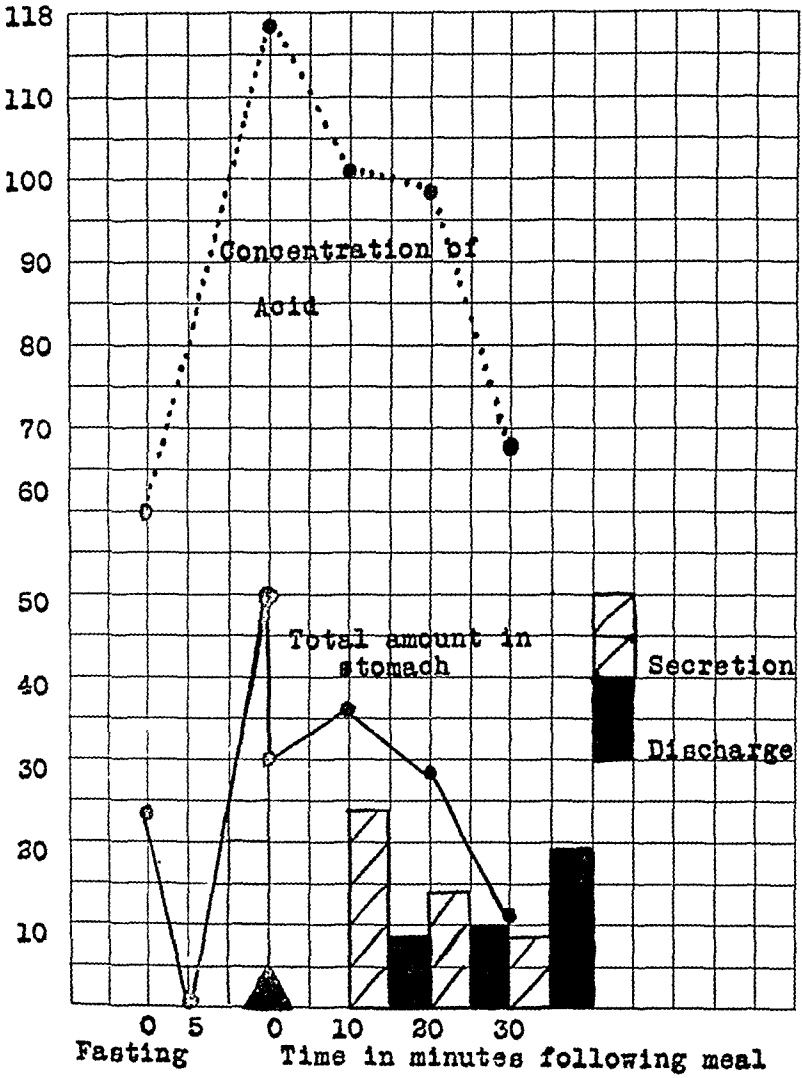


Chart 9—Findings in examination 7

TABLE 9—Results in Examination 7

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Contents, Cc	Specimen Returned, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl amidoazo-benzene	Phenolphthalein	Phenolphthalein					Maximum, Cc	Minimum, Cc	Average, Cc		
1	Fasting	24 cc fluid and mucus	1.10	48	60										60
2	Fasting, 5 minutes after meal	Nothing obtained													
3	Immediately after meal	Clear fluid	1.80	22	26		30	10	20	78					118
4	10 minutes after meal	Clear fluid	1.15	55	61		36	11	25	30	26.0	23.0	24.5	8.5	101
5	20 minutes after meal	Clear fluid	1.10	78	84		29	9	20	15	14.0	11.0	14.0	10.0	98
6	30 minutes after meal	Clear fluid	1.20	55	61		9			9 ?	13.0	1.0	8.5	18.5	67

A W, a man, aged 47 Diagnosis Hysteria, no evidence of organic disease

Total fasting contents
Fasting secretion (10 minutes)
Total secretion (30 minutes)
Largest amount secreted in 10 minutes
Largest amount in stomach during test

Comment Following test meal there was a prompt secretion of extremely acid juice in moderate amount, this steadily decreased in amount and acidity, and stomach, which emptied rapidly, was void in 30 minutes, very slight amount of fasting secretion of moderate acidity

Stomach "empty"
Lowest pH (20 minutes)
Highest free acid (20 minutes)
Highest total acid (20 minutes)
Highest acidity of pure juice

30 minutes
1.10
78
84
118

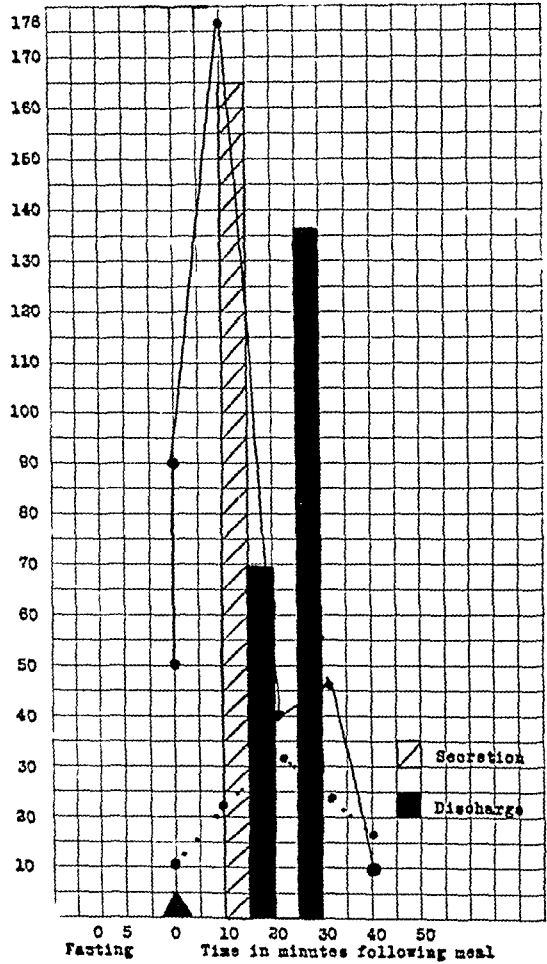


Chart 10—Findings in test 1, examination 8

TABLE 10—Results in Test 1, Examination 8

Specimen	Obtained	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
				Dimethyl amidoazo benzene	Phenolphthalein	Stomach					Max. num., Cc	Min. num., Cc	Average, Cc		
1	Fasting	Questionable amount of mucus													
2	Fasting, 5 minutes after specimen 1	Nothing obtained													
3	Immediately after meal	Clear fluid with a great deal of thin mucus	2.9	2	6	90	10	10	80	40					10
4	10 minutes after meal	Clear fluid with a great deal of thin mucus	2.0	12	20	178	12	12	164	11	200	130	165	69	22
5	20 minutes after meal	Marked bile tinged, thin mucus		18	32	40	10	10	30	0	?	?	?	136+	32
6	30 minutes after meal	Clear fluid with a great deal of mucus	1.5	16	24	46	12	12	34	0					24
7	40 minutes after meal	Clear fluid with a great deal of mucus	3.1	2	16	10				0					16

J. C., a man, aged 35. Diagnosis: Acute nephritis—convalescent, no gastric symptoms of any sort, had been on salt free diet for several weeks.

Total fasting contents
Fasting secretion during 10 minutes
Total secretion (10 minutes)
Largest amount secreted in 10 minutes
Largest amount in stomach during test

Stomach "empty"
Lowest pH (30 minutes)
Highest free acid (20 minutes)
Highest total acid (20 minutes)
Highest acidity of pure juice

20 minutes
1.5
18
32
32

Comment: A distinctly abnormal reaction, the juice consisted entirely of a thin mucus, test meal followed by a tremendous secretion of juice of very low acidity, rapid emptying of stomach.

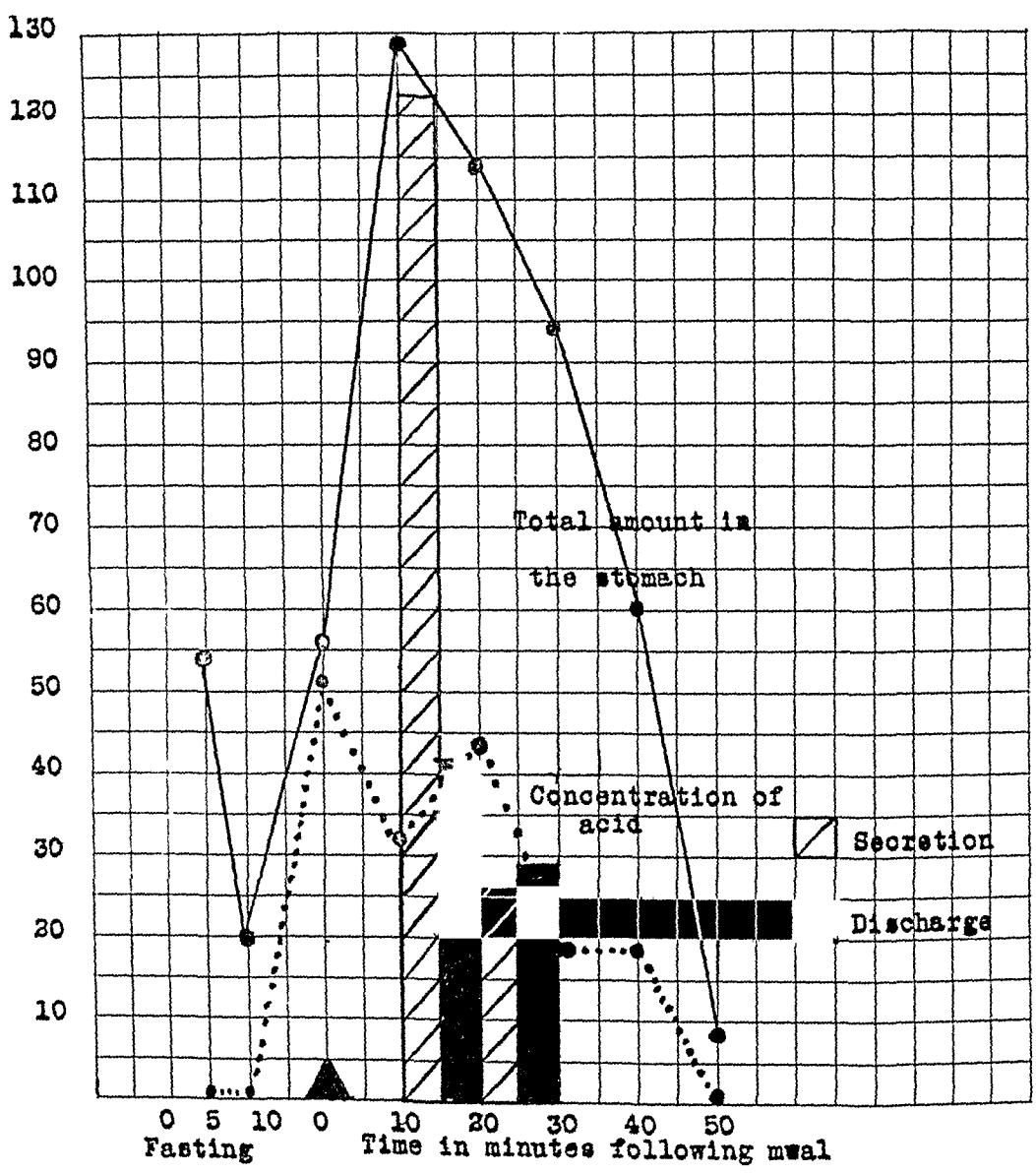


Chart 11—Findings in test 2, examination 8

TABLE 11—Results in Test 2, Experiment 8

Specimen	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid				Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenolphthalein, per Cent	Amount of Juice Secreted in Ten Minute Period			Discharged in Ten Minute Period, Cc	Acidity of Pure Juice
			Dimethyl-amidoazo-benzene	Phenolphthalein	Amount of Juice Secreted in Ten Minute Period										
					Maximum, Cc	Average, Cc									
1 Fasting															
2 Fasting, 5 minutes after specimen 1	54 cc thin mucus		0												51
3 Fasting, 10 minutes after specimen 1	20 cc thin mucus	5.6	0	6											33
4 Immediately after meal	Clear, thin mucus	1.4	24	30	56	10	46	42							
5 10 minutes after meal	Clear, thin mucus	1.7	20	28	128	12	116	10	147	98	123	41			
6 20 minutes after meal	Clear, thin mucus	1.4	26	40	114	10	104	8	29	23	26	28			43
7 30 minutes after meal	Clear, thin mucus	2.2	6	18	94	12	82	Trace							18
8 40 minutes after meal	Clear, thin mucus	1.9	6	18	60	12	48	Trace							18
9 50 minutes after meal	Clear, thin mucus	2.4			8			0							

J C, a man, aged 35 Diagnosis Acute nephritis—convalescent, no gastric symptoms of any sort, had been on salt-free diet for several weeks

Total fasting contents
Fasting secretion during 10 minutes
Total secretion (20 minutes)
Largest amount secreted in 10 minutes
Largest amount in stomach during test

Stomach "empty"
Lowest pH (20 minutes)
Highest free acid (20 minutes)
Highest total acid (20 minutes)
Highest acidity of pure juice

Comment Reaction showed essentially the same peculiarities as on previous occasion

50 minutes
1.4
26
40
43

TABLE 12—Results in Examination 9

Specimen	Amount and Appearance	pH	Titratable Acidity in Terms of Cc Tenth Normal Sodium Hydroxid			Total Stomach Contents, Cc	Specimen Retained, Cc	Amount Returned to Stomach, Cc	Concentration of Phenol-phthalein, per Cent
			Dimethyl-amidoazo-benzene	Phenol-phthalein	Hydroxid				
1 Fasting	20 cc thin fluid with bits of mucus Nothing obtained	2.1	10	26					
2 Fasting, 5 minutes after specimen 1									
3 Immediately after meal	Clear fluid Nothing obtained	4.2	0	2	25	10	15	64	
4 10 minutes after meal									

M G H, a woman, aged 28 Diagnosis Healthy control, test meal 2 years before showed "anaecidity", no definite digestive symptoms

Total fasting contents
Fasting secretion (10 minutes)
Total secretion

20 cc
0 cc
?

Largest amount in stomach
Stomach "empty"

25 cc
5 to 10 minutes

Comment Extreme sub acidity, practically no gastric secretion, marked rapidity of emptying

THE RELATION OF THE ERYTHROCYTE SEDIMENTATION REACTION TO THE ABILITY OF FLOCCULATION OF THE PLASMA AND SERUM *

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NEW YORK

Several tests have been recently advocated for the determination of "activity" in tuberculosis. The more prominently mentioned are the Frisch and Starlinger,¹ Gerloczy,² Mátefy,³ Darányi,⁴ and erythrocyte sedimentation⁵ reactions. These tests are not specific for tuberculosis and are obtainable in all conditions in which there is an accompanying tissue destruction, their utility being comparable to that of a clinical thermometer. We have had occasion to observe the sedimentation reaction on several hundred tuberculous patients and have been impressed with its usefulness in gaging the toxicity of a tuberculous process. When used in conjunction with other clinical and laboratory means of investigation, the test offers a valuable addition to the study of a patient's progress. The results that have been reported from the use of the other named tests, although not as favorable as those that have been obtained with the sedimentation reaction, nevertheless seem to indicate that the physicochemical structure of the blood, especially that of the unformed elements, is modified in some way during disease, the change being more or less proportional to the severity of the disease process. Although a similarity between these tests has been noted by the originators of the several methods, they have been, with a few exceptions, applied singly with little attempt to evaluate them from a study of the same sample of blood. The present study was therefore undertaken to determine the relationship between these tests, the accuracy and ease of their execution and their relative clinical value.

The detailed procedures of the several methods are obtainable in the original papers so that only a brief outline will be given here.

METHODS

Frisch and Starlinger Test—Two-tenths cubic centimeter of citrated plasma is added to an equal amount of concentrated sodium chloride solution, shaken once and the degree of flocculation observed.

* From the department of surgery, Yale University School of Medicine.

1 Frisch, A. V., and Starlinger, W. *Med Klin* **18** 247 (Feb 19) 1922.

2 Von Gerloczy, G. *Klin Wchnschr* **1** 2134 (Oct 21) 1922.

3 Matefy, L. *Med Klin* **19** 725 (May 27) 1923.

4 Von Darányi, J. *Deutsche med Wchnschr* **48** 553 (April 28) 1922.

5 Fahraeus, R. *Biochem Ztschr* **89** 355, 1918.

at the end of three minutes. The results are designated as —, \pm , +, ++, +++ and ++++, depending on the degree of flocculation.

Geilóczy Test—Three-tenths cubic centimeter of plasma is poured into each of six test tubes containing 0.3 cc of isotonic solutions of Hoffmeister's reagents, (1) potassium sulphate, (2) potassium chloride, (3) potassium bromide, (4) potassium nitrate, (5) potassium iodide, and (6) potassium thiocyanate. The tubes are placed in a water bath at 50 C and the temperature is gradually raised to 60 C in thirty minutes. The number of tubes in which flocculation has occurred is then noted.

Darányi Test—Two-tenths cubic centimeter of serum is added to 1.1 cc of alcohol diluted with 2 per cent sodium chloride solution, shaken well and placed in a water bath at 60 C for twenty minutes. The tubes are then placed at room temperature on a dark background and observed at one-half, one, two, three and twenty-four hours for signs of flocculation, which are expressed as +, ++, +++, ++++, or —. The alcoholic reagent is prepared by adding 4.1 cc of freshly made 2 per cent sodium chloride to every cubic centimeter of 96 per cent alcohol. The exact amount of sodium chloride to be added is obtained by preliminary testing with serums of healthy controls.

Mátéfy Test—Two-tenths cubic centimeter of serum is added to 1 cc of 0.05 per cent aluminum sulphate solution, shaken once, placed at room temperature on a dark background and observed at one-quarter, one-half, and one and one-half hours for signs of flocculation. The results are read as +, ++, +++, ++++, or — if there is no flocculation at the end of the one and one-half hour period.

Sedimentation Reaction (Morris Modification)—Into a sterile 2 cc Record syringe, a solution of 3.8 per cent sodium citrate is drawn up to the 0.4 mark. Blood is then aspirated from an arm vein to the 2 cc mark, giving a dilution of 1:4. After thorough mixing, the citrated blood is poured into small Wassermann test tubes and taken to the laboratory where the blood is aspirated into long serologic pipets graduated into hundredths, placed in a rack and the layer of clear plasma observed at one, two and twenty-four hours and read directly in percentage. The two hour reading is the most significant one. The limits of normality are up to 5 per cent for men and 10 per cent for women.

We made the following minor changes from that given in the original articles. A 3.8 per cent sodium citrate solution was used instead of a 5 per cent strength for the sedimentation and plasma tests. Frisch and Stalling's \pm notation was omitted because of its unreliability in naturally opaque plasmas and also to make it easier for comparison with the other tests.

Our study comprises sixty-four cases, mainly surgical, including ten healthy controls (medical students). With few exceptions, the tests were run in duplicate and under as similar conditions regarding the time of day and meals as possible. The glassware was clean but not sterile and the tests not requiring water baths were carried out at a room temperature of from 20 to 25 C. For the comparison of the sedimentation, Frisch and Starlinger and Gerlóczy reactions, 8 cc of venous blood was aspirated into a 10 cc Record syringe containing 2 cc of 3.8 per cent sodium citrate solution which gave the required 1:4 dilution. After two pipetfuls were removed for the sedimentation reaction, the remainder was centrifugated for one-half hour, the plasma decanted and used for the remaining tests. For the comparison of the sedimentation, Matéfy and Darányi reactions, 10 cc of blood were used of which 3.2 minims were removed for sedimentation, the remainder being allowed to clot overnight in an ice box and the serum thus obtained used for the other tests. For the comparison of all five tests, about 18 cc of blood was used. The sedimentation pipets were placed in a specially constructed stand, the base of which was covered with a rubber mat, the pipets being firmly pressed against the mat by heavy elastic bands.

Before we proceeded with our tests, it seemed desirable to note the effect of the caliber of the pipets on the sedimentation speed. Repeated comparisons of 8 pipets ranging in lengths between 17.2 and 26 cm gave differences at the end of two hours of about 2 per cent. The source of error due to small variations in pipets was therefore slight and became less with the use of pipets of more approximating sizes (from 19 to 21 cm). This was corroborated subsequently by many duplicate sedimentation tests that were observed during the course of our experiments, the variations between readings averaging about 1 per cent, the greatest 3.5 per cent. Our results are in agreement with those of Horvat⁶ and Berczeller and Wastl,⁷ who found the longer and narrower tubes to give higher readings, and also with the observations of Westergren⁸ and Fischel⁹ to the effect that the height of the column is of more practical importance than the internal diameter of the tube.

Simultaneous comparisons were also made of the methods suggested by Peschel,¹⁰ Morriss,¹¹ and Fischel⁹ to determine if they could be compared on the percentage basis that the authors recommend.

6 Horvat, A. *Munchen med Wchnschr* **69** 1729, 1922

7 Berczeller, L., and Wastl, H. *Biochem Ztschr* **146** 370, 1924

8 Westergren, A. *Klin Wchnschr* **1** 1359 (July 1) 1922

9 Fischel, K. *Am Rev Tuberc* **10** 606 (Jun) 1925

10 Peschel, G. *Beitr z Klin d Tuberk* **58** 195, 1924

11 Morriss, W. H. *Am Rev Tuberc* **10** 431, 1924

Tubes 1 and 2 of approximately the same length but of different diameters and volumes gave at two hours 27 and 25.5 per cent, respectively. This again indicates the importance of the height of column in contrast to lumen and volume. Tubes 2 and 3, each containing 2 cc of blood, gave 25.5 and 35 per cent. It is therefore evident that the difference in length of the tubes is too great to give comparative values although there is a distinctly greater millimeter drop in tube 2. That this discrepancy is chiefly due to the length is shown by comparing tubes 3 and 6, which are of the same length but of different diameters and volumes, but that the volume is also a factor to be considered is seen from the higher reading in tube 5, which contains less blood. The sedimentation percentage in the Sahli hemoglobinometer tube (tube 4) was greater than in the others. It would seem, therefore, that with a constant quantity of blood small variations in the length and lumen of tubes of any given method can cause only slight degrees of error but that the comparison of methods which use pipets of wholly different

TABLE 1—*Dog's Blood*

Experiment	Method	Volume, Cc	Size Pipets	Sedimentation					
				1 Hour		2 Hours		2½ Hours	
1	Morriss	1.0	19.6 × 0.2 cm	31 mm	15.5%	54 mm	27%	76 mm	38%
2	Fischel	2.0	20 × 0.35 cm	30 mm	15%	51 mm	25.5%	72 mm	36%
3	Fischel	2.0	10 × 0.5 cm	25 mm	25%	35 mm	35%	48 mm	48%
4	Fischel (Sahli tube)	2.0	5.5 × 0.7 cm	20 mm	36%	25 mm	46%	32 mm	62%
5	Miscellaneous	1.2	10 × 0.4 cm	26 mm	26%	39 mm	39%	52 mm	52%
6		2.3	10 × 0.55 cm	23 mm	23%	34 mm	34%	48 mm	48%

dimensions and volumes is not possible even on a percentage basis. We obtained similar results with the use of larger amounts of dog's blood as well as with human blood.

The simplicity of making readings directly in percentage without the use of a millimeter scale and time consuming interpolations makes the Morriss modification superior to the one suggested by Fischel, the blood column in the Sahli tube when filled to the 100 mark only reaches to about 5.5 cm in height, and this short distance divided into 100 equal parts is a considerable source of error since the meniscus alone may involve several divisions.

The sedimentation, Frisch and Starlinger, and Gerlőczy reactions are arranged in table 2 to allow a better comparison of the results. It will be observed that with the exceptions of cases 12, 14, 20 and 22, there is a definite parallelism between sedimentation reaction and the heightened flocculating power of the plasma. The Frisch and Starlinger test is subject to individual interpretation and with naturally opaque plasmas this is a considerable source of error. The Gerlőczy test requires more time but the readings can be made more accurately than those of the Frisch and Starlinger test. By running double tests, a

TABLE 2—Comparison of Sedimentation, Frisch and Starlinger, and Gerloczy Reactions*

Ex- peri- ment	Age	Sex	Clinical Diagnosis and Condition	Sedimentation per Cent			Frisch and Star- linger	Gerloczy		
				1 Hour	2 Hours	24 Hours				
1	22	♂	Medical student	1	1 5	17	—	+	—	—
2	23	♂	Medical student	1	2	25	—	+	±	—
3	22	♂	Medical student	2	5	29	—	+	—	—
4	21	♂	Medical student	3 5	9	37	—	+	±	—
5	62	♂	Hypertrophy of prostate	4	10 5	40	+	+	+	—
6	15	♀	Chronic renal stone ques- tionable renal stone	3 5	10 5	43	—	+	+	—
7	22	♀	Chronic appendicitis, enterop- sis and congenital adhesions appendectomy 8 days previ- ously T, P, R, normal	4 5	11 5	37 5	—	+	±	—
8	37	♂	Congenital adhesions ptosis of cecum, exploratory laparotomy, 13 days previously, T, P, R,	6	14	43	—	+	±	—
9	31	♀	Basal cell epithelioma of face 3 months after excision, T, P, R,	8	17	47	+	+	+	—
10	28	♂	Hypophyseal tumor enucleation of adenoma of pituitary gland 2 months previously, T, P, R	8	19	44	+	+	+	—
11	36	♂	Osteomyelitis of left femur re- moval of sequestrum and cu- rettement 1 month previously condition good	9 5	21	48	+++	+	+	+
12	70	♀	Tuberculosis of hip Wassermann reaction ++++ ankylosis of hip 6 weeks previously	12	26	53	++	+	+	—
13	56	♂	Fracture of neck of femur, plas- ter cast 5 months, T, P, R	17	30	50	+	+	+	—
14	32	♂	normal	21	37	59	++	+	+	—
15	24	♀	Impysemia and chronic bron- chitis moderate arteriosclerosis	22	38 5	60	+++	+	+	—
16	21	♂	Duodenal ulcer, pyloroplasty 3 weeks later	29	41 5	68	++++	+	+	—
17	39	♀	Anal fissure, Wassermann reac- tion ++++ T 99 6	23	43	65 5	+++	+	+	—
18	66	♂	Clinical condition not diagnosed Tuberculosis of spine, T, 99,	35	53	67 5	++++	+	+	—
19	61	♂	plaster cast 2 weeks Hypertrophy of prostate, peri- neal prostatectomy 9 days previously	48	56	62	++++	+	+	—
20	60	♀	Acute appendicitis with abscess formation operation 1 month previously wound discharging	46	62	68	++++	+	+	—
21	29	♂	Carcinoma of breast with metas- tases radical operation 3 weeks previously	38 5	50	58	+++	+	+	—
22	28	♂	Chronic empyema with discharg- ing sinus resection of four ribs 2 weeks previously	35	53	67 5	++++	+	+	—
23	37	♂	Deep abscess of thigh two weeks after incision and drain- age T, 100	48	56	62	++++	+	+	—
24	52	♂	Advanced pulmonary tuberculo- sis T, 98 4 R 20, P, 90, weight, 90 pounds (40 8 kg), sputum + died 1 week later Empyema of gallbladder chole- cystectomy and drainage 3 weeks previously T, 101 P 100	46	62	68	++++	+	+	—

* In this and the following tables ♂ indicates male, ♀, female T, temperature, P, pulse, and R respiration

finer differentiation could be obtained between the positive and the negative tubes. We also found it helpful to allow the tubes to stand overnight at room temperature and allow the diffuse precipitate to settle at the bottom. This checked our previous readings without seeming to affect the negative tubes. The Frisch and Starlinger test had to be read at the end of three minutes since the flocculation power of the plasma increased on standing. The four healthy controls and cases 6 and 7 gave readings within normal limits with the sedimentation reaction and, with one exception, with the Frisch and Starlinger test, but all gave + or ++ with the Gerlőczy test, the latter finding being contrary to the results obtained by Gerlőczy who obtained no flocculation with normal plasmas. The sedimentation reaction gave no difficulty in setting up the pipets or in taking readings. The source of error of this test due to variations in the number and size of erythrocytes and the hemoglobin content will be discussed more fully later.

The Frisch and Starlinger test was found by its authors to parallel the sedimentation reaction and to depend primarily on the fibrinogen content of the plasma, a slight cloudiness or \pm indicating less than 0.2 per cent and a strong flocculation or ++++, more than 0.4 per cent fibrinogen. Deusch¹² found agreement between the sedimentation reaction, Frisch and Starlinger and the globulin content of the serum in cases of tuberculosis. This author also mentions the source of error due to the difficulty of interpretation of flocculation intensities. Weise,¹³ on the basis of more than 2,000 tests on 500 tuberculous children and 150 adult women, recommends a combination of the sedimentation and Frisch and Starlinger tests in following the course of the disease. The relationship between the sedimentation, Frisch and Starlinger tests and his own test was noted by Gerlőczy. Torok¹⁴ found the Gerlőczy reaction positive in tuberculosis and syphilis and negative in rickets, while parenteral infections caused less change in the colloid lability of the plasma of breast fed children than of those artificially fed. The Gerlőczy reaction was also noted in acute infectious diseases and tuberculosis by Cahn-Bronner.¹⁵ In the cases of tuberculosis, it allowed prognostic decisions.

An excellent review of the sedimentation reaction and its applicability in tuberculosis is to be found in a recent monograph by Westergren.¹⁶

12 Deusch, G. *Deutsche med. Wchnschr.* **51** 229 (Feb. 6) 1925.

13 Weise, L. *Beitr. z. Klin. d. Tuberk.* **56** 367, 1923-1924.

14 Torok, G. *Monatschr. f. Kinderh.* **28** 14, 1923.

15 Cahn-Bronner. *Verhandl. d. deutsch. Gesellsch. f. inn. Med.*, 36 Kong., 1924.

16 Westergren, A. *Ergebn. d. inn. Med. u. Kinderh.* **26** 577, 1924.

Table 3 gives a comparison of the sedimentation, Mátéfy and Darányi reactions. In general, the Mátéfy reaction shows increased flocculation accompanying increased sedimentation but the results are not as marked as those obtained with the plasma tests. This is probably

TABLE 3—Comparison of Sedimentation, Mátéfy and Darányi Reactions

Ex- peri- ment	Age	Sex	Clinical Diagnosis and Condition	Sedimentation, per Cent			Mátéfy	Darányi
				1 Hour	2 Hours	24 Hours		
25	22	♂	Medical student	15	3	17	—	—
26	24	♂	Medical student	1	3	25	—	—
27	26	♂	Medical student	2	5	35	—	—
28	23	♂	Medical student	5	12.5	36	—	—
29	18	♂	Deviation of nasal septum	2	7	36.5	—	—
30	37	♂	Basal cell carcinoma of face 4 months after operation, wound healed	4	8	31	+	—
31	17	♂	Fracture of fibula T, P, R, normal	2	9	36.5	—	—
32	17	♂	Chronic constipation	4	9.5	39.5	+	—
33	61	♂	Cerebral arteriosclerosis (?), T, P, R, normal	4	10	40	—	—
34	22	♂	Tuberculosis of kidney, nephrectomy 4 months previously, T, P, R, normal, chest negative	4	10	40	—	—
35	20	♂	Crushing injury to great toe with granulation of distal phalanx	4	10.5	36.5	++	—
36	52	♂	Hemorrhoids 20 days after operation	5	17	37	+	—
37	70	♂	Diverticulum of bladder multiple renal calculi and left hydronephrosis	6	17.5	44.5	+	—
38	21	♂	Pilonidal sinus 2 weeks after excision	5.5	18	40	+	—
39	55	♂	Fistula of urethra and perineum 5 weeks after suprapubic cystotomy T, P, R, normal	5.5	18	40	+	—
40	36	♂	Tuberculosis of hip, Wassermann reaction + + + +, ankylosis of hip 2 months previously	14.5	20	44	+	—
41	64	♂	Chronic osteomyelitis of femur and tibia 5 months after amputation of leg	12	21	41	++	—
42	31	♂	Acute appendicitis 11 days after appendectomy T, P, R, normal	10.5	25	57	+	—
43	38	♀	Chronic appendicitis adhesions about cecum 8 days after appendectomy	13	27	53.5	+	—
44	49	♂	Renal stone removed 8 days later, died of pneumonia 2 weeks after operation	11	31	51	+	—
45	30	♂	Cervical lymphadenopathy, probably Hodgkin's T, P, R normal	15	31	56	++	—
46	46	♂	Tuberculous peritonitis 18 days after exploratory laparotomy, slight fever	20	36	62	++	—
47	73	♀	noon temperature bilization	21.5	37.5	63	++	—
48	53	♀	Recurrent spindle cell sarcoma of buttock operation 1 year previously	27	41	62	++	—
49	29	♂	Chronic empyema with discharging sinus 7 weeks after resection of 4 ribs, T, P, R, normal	36.5	44	52	++++	—
50	18	♀	Acute appendicitis 3 days after appendectomy T, 100, P, 100	27	45	62	++	—
51	28	♂	Deep abscess of thigh, 1 month after incision and drainage T, 100, P, 100	40	49	62	+++	—
52	52	♂	Empyema of gallbladder cholecystectomy 5 weeks previously, drainage slight temperature	35	57.5	66	++	—
53	57	♂	Carcinoma of stomach with metastases T 100	45.5	59	68	+++	—

owing to the fact that the plasma tests include the most labile component, the fibrinogen, as pointed out by Sachs and von Oettingen¹⁷ whereas the serum reactions depend on an increased globulin-albumin ratio

¹⁷ Sachs, H, and von Oettingen, K (March 25) 1921

The Darányi reaction was found negative in all the cases studied, the serums on removal from the water bath showed various degrees of opalescence but no definite flocculation.

Diverse results have been obtained with the Mátéfy reaction by different investigators. Some of the discrepancies are due to the difficulty of making accurate readings while others are due to the uncertainty of the test to indicate tissue destruction in pathologic conditions and the frequency of positive reactions in healthy controls. Kromeke¹⁸ corroborated Mátéfy's findings in tuberculosis and found the reaction positive in syphilis, malignant tumors and in other processes accompanied by cell destruction, while healthy individuals or those with superficial catarrhal processes gave negative results. Lukács¹⁹ obtained + and ++ flocculations among healthy children and although +++ and ++++ readings were found in tuberculosis, syphilis, acute infections and chronic inflammations, the test lost much of its value since only the two higher gradations were of any significance. Poor results with the Mátéfy reaction were reported by Basch,²⁰ who found no relationship between the test and the extent of the disease process or the degree of activity. Winkler and Gerth²¹ obtained negative reactions in 10 per cent of active tuberculous cases and positive ones in 25 per cent of healthy controls, while Beekmann²² and Buttner²³ noted positive reactions in about one-half their healthy controls. The sedimentation reaction permitted a better follow-up of the therapeutic effects on the tuberculous process. The sedimentation reaction is recommended by Zwerg²⁴ as a much simpler and more reliable test than the Mátéfy reaction. Gaeltgens and Gockel²⁵ compared the sedimentation with the Mátéfy reaction on 187 adults with tuberculosis and found the Mátéfy reaction frequently positive in inactive and negative in active cases. Positive sedimentation reactions were of considerable value in prognosis as well as in diagnosis when other conditions giving positive reactions could be excluded but a negative outcome did not exclude an active tuberculosis.

The difficulty of interpreting flocculation intensities even after stated time intervals accounts to a greater extent for the difference in the results reviewed. Our own observations agree more with those of Zweig since we had only one ++++ and four +++ reactions in forty observations, but we did not obtain any positive reactions with serums of

18 Kromeke, F. *Deutsche med Wchnschr* **50** 231 (Feb 22) 1924

19 Von Lukács, J. *Med Klin* **20** 788 (June 8) 1924

20 Basch, F. *Med Klin* **20** 384 (March 23) 1924

21 Winkler, W., and Gerth, H. *Med Klin* **20** 1080 (Aug 3) 1924

22 Beekmann, A. *Deutsche med Wchnschr* **50** 1537 (Nov 7) 1924

23 Buttner, H. E. *Munchen med Wchnschr* **72** 50 (Jan 9) 1925

24 Zwerg, H. *Deutsche med Wchnschr* **51** 353 (Feb 27) 1925

25 Gaeltgens, W., and Gockel, M. *Beitr z Klin d Tuberk* **59** 36, 1924

healthy controls We were able to differentiate in the Matéfy reaction two forms of flocculation, one manifested itself by a diffuse finely dispersed, granular turbidity which settled slowly to the bottom Such flocculations frequently accompanied high sedimentation values The reaction was called positive when the floccules had settled sufficiently to show a clear zone of serum above This usually took from twenty to thirty minutes or +++ Centrifugating a few specimens verified our interpretation The second form of flocculation was observed in serums of low flocculating power In these cases, large, uneven flakes were observable at the bottom of the test tube in from one to one and one-half hours in a previously clear or slightly turbid serum Normal serums showed flocculations in from two to three hours

The Darányi²⁶ reaction was noted by its originator to coincide to some extent with the sedimentation reaction and the increased precipitation of plasma and serum by various methods, all being measures of tissue destruction His results have been corroborated by Duzar²⁷ in tuberculous children Kremer²⁸ found several cases of 102 studied which did not show flocculation but in general the reaction coincided with the stage of the disease, being weakly positive in the first and second stages and strongly positive in the third stage The Darányi reaction was obtained by Kromeke²⁹ in the primary and secondary stages of syphilis, but in eighty-two cases of uncomplicated, latent or congenital, seropositive syphilis it was negative, indicating little toxic formation in the organism Kruchen³⁰ used the Darányi reaction in 300 cases of tuberculosis and in 200 it was compared with the sedimentation reaction In 23 per cent, the Darányi reaction gave wrong results and, because of the insufficient number of gradations, he did not find the test as practical as the sedimentation reaction, although in the latter he found the red blood cells to be a factor Nassau and Hendelsohn³¹ obtained positive reactions in acute intestinal intoxications in children Sauvan and Chiappe³² noted the reaction in only two conditions, in sixty-four cases of tuberculosis and in ten of cancer In all other conditions, including pneumonia, pleurisy, typhoid, malaria and syphilis, the test always was negative These authors believe the test can be used in differential diagnoses in these two conditions Mendel³³ obtained positive reactions in other diseases besides tuberculosis, while

26 Von Daranyi, J. *Wien klin Wchnschr* **35** 885 (Nov 9) 1922

27 Duzar, J. *Jahrb f Kinderh* **102** 69 (May) 1923

28 Kremer, W. *Ztschr f Tuberk* **38** 428, 1923

29 Kromeke, F. *Med Klin* **19** 310, 1923

30 Kruchen, C. *Beitr z Klin d Tuberk* **58** 301, 1924

31 Nassau, E, and Hendelsohn, W. *Klin Wchnschr* **2** 1835 (Oct 1) 1923

32 Sauvan, A, and Chiappe, X. *Compt rend Soc de Biol* **90** 1265, 1267 (May 16) 1924

33 Mendel, L. *Jahrb f Kinderh* **106** 15 (May) 1924

Steinbrinck³⁴ prefers the use of plasma for the testing of colloid lability because serum lacks the most labile component, fibrinogen

From the review of some of the conflicting results that have been obtained with the Darányi reaction and from our own observations, it would appear that the test, in its present condition, is not suited for the determination of tissue destruction. It is also obvious that a test that tends to become more positive in conditions of cachexia cannot be of much help in the early diagnosis of disease even if it were to possess specificity. For the same reason it loses in value as a finer indicator of tissue destruction. From the recent work of Furth and Bluh³⁵ and Dalla Volta and Benedetti,³⁶ it seems that when minute amounts of alcohol are added to serum, marked changes are produced in the physico-chemical structure of the latter and these observations are confirmed clinically by Rusznyak, Barat and Kurthy,³⁷ who believe that the Darányi reaction does not depend on the amount of globulin but that it is a manifestation of hitherto unrecognized changes in the serum. The problem requires more study.

The mechanical difficulties are greater with the Darányi than with the other reactions. It is necessary to titrate accurately the amount of 2 per cent sodium chloride solution to be added to the alcohol reagent by preliminary testing of the serums of healthy controls. Darányi used 4.1 cc. 1 cc. of 96 per cent alcohol solution. We used 4.2 cc. 1 cc. of 96 per cent alcohol solution but only three of six serums of healthy controls showed any consistency in the flocculation with the different concentrations.

Table 4 is a comparative study of all five tests. The results agree with those tabulated previously with the exception of cases 60 and 61, which gave a negative, and case 64 which gave a ++ Mátéfy reaction in the presence of marked increases in the sedimentation, Frisch and Starlinger and Gerlőczy reactions. Duzái and Rusznyak³⁸ studied the colloid lability of infant's blood by means of the sedimentation, Frisch and Starlinger, Gerlőczy and Darányi reactions as well as the total proteins, albumin, globulin and fibrinogen fractions and found the first three tests to run parallel while the Darányi test was frequently negative when the others were positive. The plasma tests were found related to the fibrinogen and the Darányi test to the globulin fractions.

The theories that have been advanced in explanation of the sedimentation reaction are intimately related with those suggested for the

34 Steinbrinck, W. *Ztschr. f. klin. Med.* **100** 39 (May) 1924.

35 Furth, R., and Bluh, O. *Kolloid Ztschr.* **34** 129, 1924, *Phys. Abstracts* **9** 287, 1924.

36 Dalla Volta, A., and Benedetti, P. *Arch. di sc. biol.* **5** 287, 1923-1924, *Physiological Abstr.* **9** 421, 1924.

37 St. Rusznyak, Barat, L., and Kurthy, L. *Klin. Wchnschr.* **2** 1479, 1923.

38 Duzar, J., and St. Rusznyak. *Monatschr. f. Kinderh.* **28** 25, 1923.

plasma and serum flocculation tests although the presence of red blood cells in the former complicates matters. In the case of the sedimentation reaction it is generally assumed that there is an increased agglutination of the red blood cells in rapidly sedimenting bloods, the larger clumps tending to settle more quickly to the bottom. But whether the increased agglutination is primarily due to a change in electric potential

TABLE 4—*Comparison of Five Tests*

Ex- peri- ment	Age	Sex	Clinical Diagnosis and Condition	Sedimentation, per Cent			Frisch and Star- linger	Gerloczy	Mat. & Daranyi	
				1 Hr	2 Hr	24 Hr				
54	21	♂	Medical student	1	2	23	—	+ ± — — — —	—	—
55	26	♂	Medical student	1	2.5	24	—	+ — — — — —	—	—
56	23	♂	Dislocation of semi-lunar cartilage of knee T, P, R normal	2	5	21	—	+ ± — — — —	—	—
57	36	♂	Tuberculosis of hip Wassermann reaction + + + +, ankylosis of hip 3 months previously	14	20	40	+	+ ± — — — —	+	—
58	42	♂	Chronic osteomyelitis of femur of 13 years duration 7 weeks after curetting and insertion of drains wound still discharging	10	20	41	++	+ + + — — —	++	—
59	19	♂	One day after removal of adenoids and tonsils T, 99.6 P, 90	19	34	52	++	+ + ± — — —	++	—
60	62	♂	Lacerations about head following accident T 100 P 90	22	37	54	++	+ + ± — — —	—	—
61	41	♂	Clinical condition not diagnosed abdominal and gastric symptoms red blood cells 2,800,000, hemoglobin 50% (T. J. Quist) roentgen ray examination showed a questionable duodenal ulcer	23	48	62	+++	+ + + ± — —	—	—
62	36	♂	Multiple fractures 2 months after admission wounds almost healed T, P, R normal Wassermann reaction + + + +	2	40	32	++++	+ + + + ±	++++	—
63	25	♂	Pilonidal sinus 1 day after excision and curetting T 99.6 P 100	43	53	64	++++	+ + + + +	++++	—
64	31	♂	Maxillary sinusitis T, 100 P 90 toxic symptoms	45	60	66	++++	+ + + + +	++	—

between negatively charged erythrocytes and positively charged bodies in the plasma (Fahraeus-Hober theory³⁹) or whether it is due to an increase in the fibrinogen fraction of the plasma (Frisch and Starlinger theory⁴⁰) is still debatable. Chemical studies have shown that the sedimentation reaction is accompanied by an increase in the globulin

39 Hober, R., and Mond, R. *Klin. Wchnschr.* **1** 2412 (Dec 2) 1922

40 Frisch, A., and Starlinger, W. *Med. Klin.* **17** 1147, 1177, 1921

albumin ratio,⁴¹ and this factor is considered the basis of the serum flocculation tests. Others have shown an increase in fibrinogen⁴² and this factor is the basis of the plasma flocculation tests. Still others have demonstrated increases in viscosity⁴³ cholesterol,⁴⁴ phosphorus⁴⁵ and lipase⁴⁶ which accompany these colloid lability reactions. It would seem, therefore, that with our present knowledge no single component of the blood can be held accountable for the phenomena observed but that these reactions express the total of complicated physicochemical changes that accompany disease, and various factors may play a rôle in their causation, depending on the nature, location and severity of the disease process.

The influence of the number and size of erythrocytes and their hemoglobin content on the sedimentation reaction has been the primary cause for the advocacy of testing plasma and serum instead. Buiker⁴⁷ and his pupils found that the size and hemoglobin content of the erythrocytes influenced sedimentation. Behrens⁴⁸ and Bonniger and Herimann⁴⁹ also are of the same opinion. The latter corroborated Abderhalden's⁵⁰ findings, that the various layers of red blood cells have different sedimenting properties. The question is not of great moment. On another occasion we made over 100 complete blood counts in conjunction with the sedimentation reaction and found no relation between the number and hemoglobin content of the red blood cells and the sedimentation reaction. The counts were not of cases of anemia or polycythemia and averaged between four and five and one-half millions of erythrocytes and from 70 to 80 per cent hemoglobin (Sahli method). Between such limits the red blood cell factor was of no appreciable importance. It is well known that a marked diminution of erythrocytes causes an acceleration while an abnormal increase causes a delay in the sedimentation reaction, but in such instances the blood picture would probably be of greater clinical significance than the colloid lability tests that have been suggested. Opitz

41 Salomon, A. *Ztschr f klin Med* **99** 329, 1924

42 Seki, T. *Biochem Ztschr* **143** 365, 1923. Murakami, J., and Yamaguchi, T. *Ann de med* **15** 297 (April) 1924. Schindera, M. *Deutsches Arch f klin Med* **144** 113 (May) 1924.

43 Petschacher, L. *Ztschr f d ges Tuberk* **20** 284, 1923

44 Kurten, H. *Klin Wchnschr* **3** 1216 (July 1) 1924. Lasch, F. *Ztschr f d ges exper Med* **42** 548, 1924. Grossmann, H. *Ztschr f d ges exper Med* **42** 496, 1924.

45 Stern, A. *Deutsches Gesell f Kinderh* **9**, 1924

46 Lederer, M. *Monatschr f Kinderh* **27** 608 (March) 1924

47 Burker, K. *Munchen med Wchnschr* **69** 577, 1922

48 Behrens, B. *Munchen med Wchnschr* **71** 229 (Feb 22) 1924

49 Bonniger, M., and Herimann, W. *Klin Wchnschr* **3** 403 (March 4) 1924

50 Abderhalden E. *Arch f d ges Physiol* **193** 236 1921-1922

and Frei⁵¹ have shown that in children, only in anemia is there found with regularity any relationship between the sedimentation reaction and the color index of the red blood cells but that in individuals with a normal blood status, the sedimentation reaction is seldom influenced by this factor. Similar opinions are held by others.

CONCLUSIONS

1 Depending on the toxicity of a disease process, a proportional increase in the erythrocyte sedimentation reaction and the ability of flocculation of the plasma and serum, as determined by the Frisch and Starlinger, Gerlóczy and Mátéfy reactions, was found. The Daiányi reaction was negative in forty cases studied.

2 Because of its greater simplicity, accuracy and wider range of readings the sedimentation reaction seemed the most practical test to use clinically. A percentage basis suggested by Morriss offered a convenient method of noting the results.

51. Optiz, H., and Frei, M. *Jahrb. f. Kinderh.* **100**: 55, 1923.

THE SEASONAL VARIATION IN THE ONSET OF ACUTE DIABETES

THE AGE AND SEX FACTORS IN 1,000 DIABETIC PATIENTS *

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It is evident to those who see a considerable number of patients with diabetes that, if the disease is classified according to its actual onset, two main forms are encountered. One form begins acutely and is ushered in with the abrupt appearance of the symptoms familiar to every physician. The course is usually downward, this form usually attacks persons less than 40. The other may be so gradual in onset and course in some instances that it is impossible to determine the date of origin. The presence of sugar in the urine is discovered quite by accident. Diabetes which comes on insidiously is ordinarily associated with obesity and arteriosclerosis.

In taking the history of patients with acute diabetes, when the date of onset can be fixed with reasonable certainty, I was impressed by the fact that there are certain seasons of the year when the onset of the disease is more common. With the idea of confirming this impression, the case records of 1,000 patients with diabetes were studied. In this group there were 317 cases that could be classified as acute and in which the disease began so suddenly that there could be no question as to the time. Case records were discarded when there was any question about this point. In examining these records, I was constantly mindful of the possibility that a mild chronic case of diabetes might suddenly become more severe from some cause and the usual symptoms of diabetes not be forcibly brought to the patient's attention until then.

The results of classifying the cases according to the month of onset of disease are shown (fig 1). It appears that acute diabetes is most likely to be precipitated during the fall, winter and spring.

Seventy-seven and three-tenths per cent of the patients studied came from Minnesota, Montana, Michigan, Nebraska, the Dakotas, Iowa, Wisconsin, northern Illinois and central southern Canada. The possible relationship between the onset of acute respiratory infections and the onset of the diabetes is obvious. The states mentioned have a long winter season, and the inhabitants are therefore exposed to longer seasons when colds in the head, acute bronchitis, influenza and the like are prevalent. Often a patient said that his diabetes appeared immediately after such an infection and in most cases a history of preceding infection was obtained, although, in many it was thought too trivial to

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require a physician. In some cases the diabetes started abruptly without a preceding infection. It is probable, however, that a disproportionate number of these patients had not observed their condition carefully.

A long winter season forces many persons to lead sedentary lives and it is doubtful whether they deliberately eat less because they are less active. Therefore, a possible sequence of events is as follows: one person, on account of heredity or other reasons, may be slightly more susceptible to diabetes than another. During a period of enforced idleness he eats as much food as during his period of activity. He develops an acute respiratory infection. This combination of events is sufficient to throw the balance in favor of diabetes. It is interesting in this connection to note that for 1922 the death rate from diabetes for the reported northern states was considerably greater than for the reported southern states. To quote the twenty-third annual report of the department of commerce:

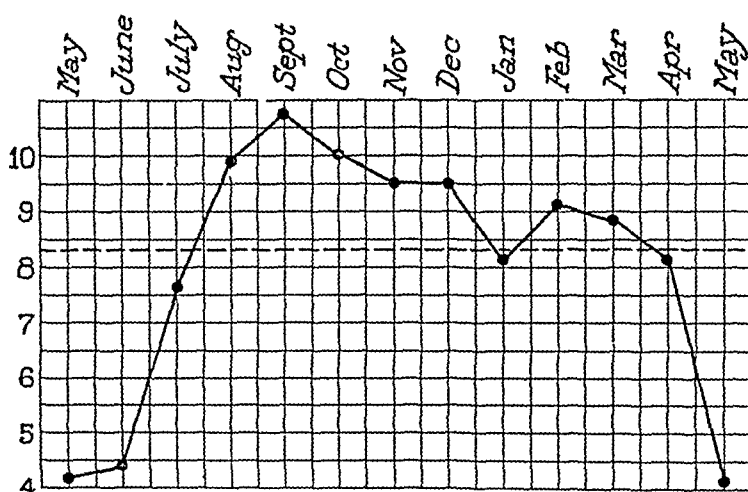


Chart 1—Percentage of 317 cases of acute diabetes according to month of onset

The states with the highest death rate from diabetes in 1922 are New Hampshire (311 per hundred thousand), Vermont (27), New York (269), Maine (253), and those with the lowest rates are Mississippi (73), South Carolina (76), Tennessee (77), Kentucky (81), and North Carolina (87).

If one divides the United States at 37 degrees latitude he finds that the states above the line have a diabetic death rate of 19.3 per hundred thousand and the states below a death rate of 8.5. It might be asserted that this discrepancy is due to the greater reliability of the mortality statistics of the northern states, but I cannot believe that this accounts for it entirely.

Seventy per cent of the diabetic patients coming to the clinic live in towns of 10,000 population or less. Thirty-one per cent live in places of less than 1,000 population (table 1). Whether all our patients developed diabetes in these environs cannot be determined. They probably did not. However, considerably more than half of all the patients

coming to the Mayo Clinic live in rural districts This fact makes enforced idleness during the winter months seem the more likely

In order to discover at what time of life a person is most likely to develop diabetes, a series of 1,000 patients of all types was studied with reference to their age at the time the disease was discovered Included in this group of patients are a number with the onset of the diabetes not accurately fixed This applies particularly to older patients Nearly

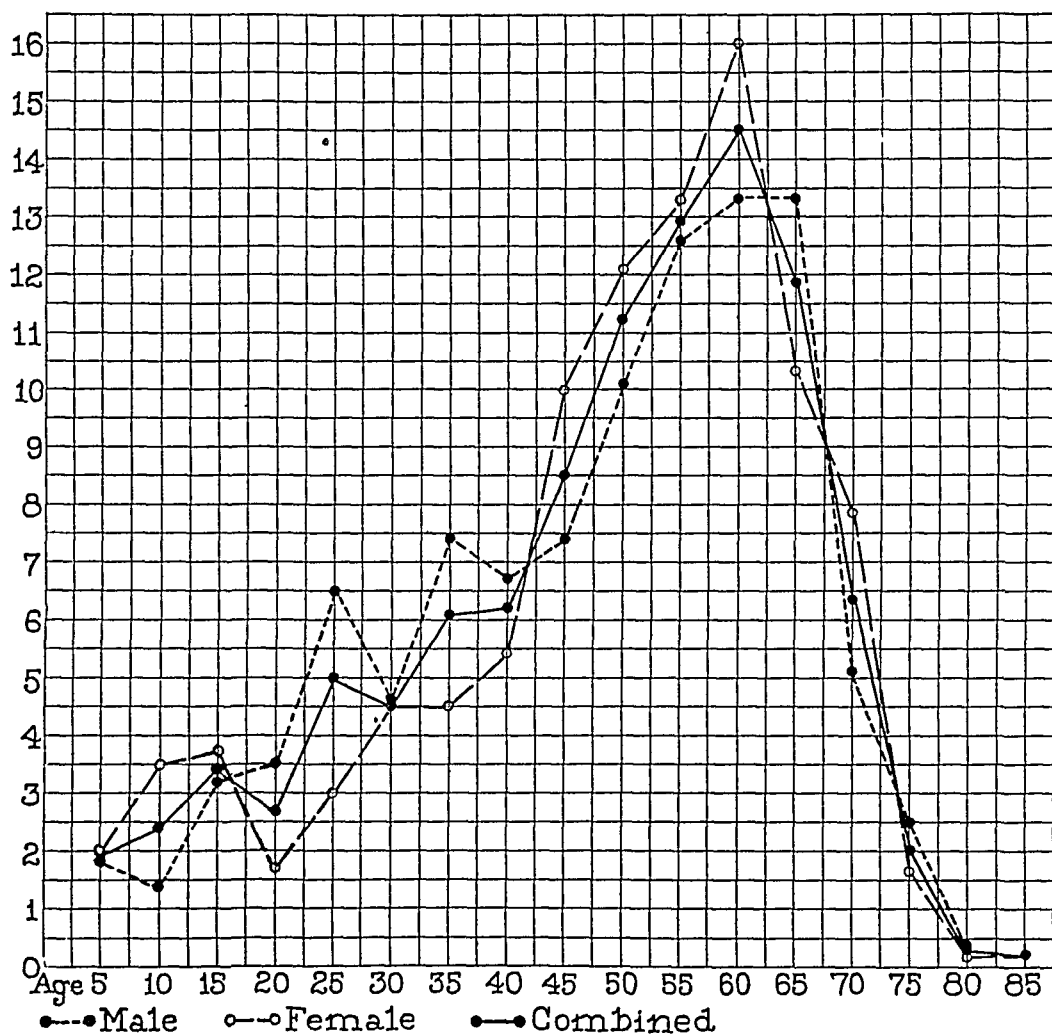


Chart 2—Percentage of 1,000 cases of diabetes at various ages

every patient, however, was able to tell at least at what age his diabetes was discovered

In charting these according to half decades (fig 2), it appears that there is a gradual increase in diabetes with increase in age, in a population largely rural, up to the age of 60 Beyond this point there is an acute decline in the incidence

The data reveal that 593 of the 1,000 developed diabetes after the age of 45 The percentage of diabetes in patients more than any given age is noted in table 2

The sex distribution in the 1,000 patients under consideration for all ages was 58 per cent males and 42 per cent females

SUMMARY

Diabetes of the acute progressive form, as seen in the middle west, is a disease that begins more frequently in the fall, winter and spring than in the summer. A more sedentary life and a greater incidence of acute respiratory infections during this period suggest a combination of circumstances favorable for the precipitation of diabetes. Diabetes is

TABLE 1—*One Thousand Diabetic Cases Grouped According to Size of Town*

Size of Towns	Cases
1 to 1 000	326
1,000 to 2,500	185
2,500 to 10 000	172
10 000 to 100 000	196
Above 100 000	121
Total	1 000

TABLE 2—*Age Incidence*

Years	Males		Females		Total Per Cent
	Cases	Per Cent	Cases	Per Cent	
1-5	10	1.8	9	2.0	1.9
6-10	9	1.4	15	3.5	2.4
11-15	18	3.2	16	3.7	3.4
16-20	20	3.5	7	1.7	2.7
21-25	37	6.5	13	3.0	5.0
26-30	26	4.6	19	4.5	4.5
31-35	42	7.4	19	4.5	6.1
36-40	39	6.8	23	5.4	6.2
41-45	42	7.4	43	10.0	8.5
46-50	60	10.1	52	12.1	11.2
51-55	72	12.6	57	13.3	12.9
56-60	76	13.3	69	16.0	14.5
61-65	75	13.3	44	10.3	11.9
66-70	29	5.1	34	7.9	6.3
71-75	14	2.5	7	1.6	2.0
76-80	2	0.4	1	0.2	0.3
81-85			1	0.2	0.2
Total	571		429		
Total patients more than 10 years of age					Per Cent 95.7
Total patients more than 20 years of age					89.6
Total patients more than 30 years of age					80.1
Total patients more than 40 years of age					67.8
Total patients more than 50 years of age					48.1

a disease that gradually increases in incidence with age up to 60, after which there is a sudden decline in frequency, due probably to the falling off of the population of persons over 60. It is slightly more prone to afflict males than females. The figures here reported are based on studies of diabetes as seen in the middle west. General conclusions, however, should not be drawn from the study of patients from one section of the country. Only by combining observations made in different sections of the country can any real estimate of facts be properly made.

Book Reviews

INTRODUCTION TO DERMATOLOGY By SIR NORMAN WALKER Eighth Edition
New York William Wood & Co, 1925

This new edition of Sir Norman Walker's Introduction to Dermatology should be a welcome addition to every practitioner's library. Like its predecessors it is a book that is a pleasure to read. It is written in an easy, intelligible style and gives the reader a clear conception of the commoner skin conditions.

Many additions have been made to the last edition. The text is well illustrated with photographs and colored plates and the print is large and easily read. It sums up in a clear concise manner the teachings of the Edinburgh school and should be read by every physician interested in dermatology.

SCIENTIFIC REPORTS FROM THE GOVERNMENT INSTITUTE FOR INFECTIOUS DISEASES,
TOKIO IMPERIAL UNIVERSITY Director, MATARO NAGAYO Edited by
YONEJI MIYIGAWA Vol III Tokyo Shirokane-Daimachi, 1924

This volume covers a wide range of activities, including bacteriology, chemistry and pathology, and the imposing character of the work reported cannot fail to impress one with the great importance of this research institute. The present report contains nineteen articles covering 241 pages, with profuse illustrations. Many of these papers are simply resumes of one or more far more elaborate articles originally published only in Japanese. Here all are translated into English or German, with one in French.

Of special note is the summary of the research by a number of workers on tsutsugamushi disease. By intradermal inoculation of blood from infected patients they have reproduced the disease typically. The causative organism is proved to be nonfiltrable and nonculturable on all ordinary mediums. It can be transmitted only by the bite of a small mite, *Trombicula akamushi*. The offending organism is multiform, having monococcal, diplococcal and bacillary forms, and cannot as yet be classified zoologically. However, it bears a striking resemblance to the microcorpuscles of *Rickettsia*, although the latter is borne by a blood sucking parasite and *Trombicula* is lymph sucking.

Special mention may also be made of the paper by Ikeda showing that the immunity transmitted from mother to young is not transmitted through the placenta but through the milk in the first few days of life. The immunizing substances are not destroyed by the gastric juice of the new-born. Miyagawa and Kada's demonstration of the influence of the thymus on growth also is important. They show that small doses of thymus administered parenterally cause a remarkable increase in growth in young animals but that larger ones are toxic and retard growth. This explains many of the discrepancies in the literature.

Most of the work reported is of a high grade of importance, but space will not permit even a summary of what is already largely a condensation of far more detailed reports.

TROUBLES DE LA FONCTION GASTRIQUE ET SYNDROMES ASSOCIES CHEZ LES
TUBERCULEUX PULMONAIRES (LA TOUX EMETISANTE) By PIERRE MARSAL
Inaugural thesis at the University of Nancy Paris A Maloine et fils

This thesis is the report of a careful, thorough study of sixty-five cases in the sanatorium at Nancy in the service of Parisot. All of these were active cases of pulmonary tuberculosis that presented grave gastric symptoms. Digestive disturbances occurred in 20 per cent of all consumptives and were about

three times as common in women as in men. While fundamentally these troubles are due to the toxemia of the infection they are often brought on by overfeeding and medication. Many closed cases had gastric disturbances, showing that swallowed septic matter was not necessarily a factor.

Examination of the stomach did not as a rule show any extreme degrees of variation from the normal. In the early cases there was a hypersecretion and a hyperactivity of the gastric juices as shown by digestive tests. Roentgenoscopy generally showed a hypermotility and a marked tendency to spasm. Later in the course of the disease both the gastric motility and the secretory functions appear slightly diminished. Late cases coming to postmortem examination confirmed this picture. The mucosa was slightly atrophied and there was a subacute interstitial gastritis of low grade, this was in all probability due to swallowed septic matter, although no actual tubercles or evidences of tuberculosis of the stomach were encountered.

In the foregoing class of cases there was definite evidence of a vagotonia, which, however, was not the underlying cause. In another category, that of the postprandial vomiting, the factor of the vegetative nervous system was predominant. This syndrome occurred in 23 per cent of Marsat's cases. It is variously described as a deglutition cough, Morton's cough or vomiting cough (*toux emetisante*). The cough is undoubtedly brought on by deglutition, this cough is of such violence that vomiting is induced. Nausea is generally absent. Fundamentally the vegetative nervous system is at fault. It is an exaggeration of perfectly normal reflexes. The sensory arc of these reflexes is the vagus and the motor arc is the phrenic nerve through the superior cervical ganglion. The hypersensitive sensory arc is stimulated by swallowing, which brings on the cough, when the patient is out of breath and inspires deeply and suddenly there is a contraction of the diaphragm and abdominal walls accompanied by a negative pressure in the chest. The hypertonic stomach at this moment tends to empty itself into the esophagus.

In the therapeutics of this condition atropine has given excellent results.

THE PATHOLOGY OF TUMORS. By E. H. KETTLE, M.D., B.S., London. Second Edition. New York: Paul B. Hoeber, 1925.

As stated in the preface, the plan of this book is to provide a manual for students that will contain the generally accepted teaching on the pathology of tumors without the mass of detail necessary in a larger work of reference.

The author has no doubt succeeded in doing this and the book will serve a real need in the presentation of this subject to students, especially in primary and optional courses in pathology. For a work of this kind the illustrations are satisfactory and are relatively numerous.

There are short chapters on the etiology of cancer and on the experimental study of cancer, but most of the book is given over to the classification of tumors and a description of the standard types. Other these descriptions are so terse that they are of little or no value.

There is a brief presentation of the work of Peyton Rous and of Gye on the possible existence of an infecting virus. Apparently the monumental work of Maude Slye on the relation of heredity to cancer has been overlooked.

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